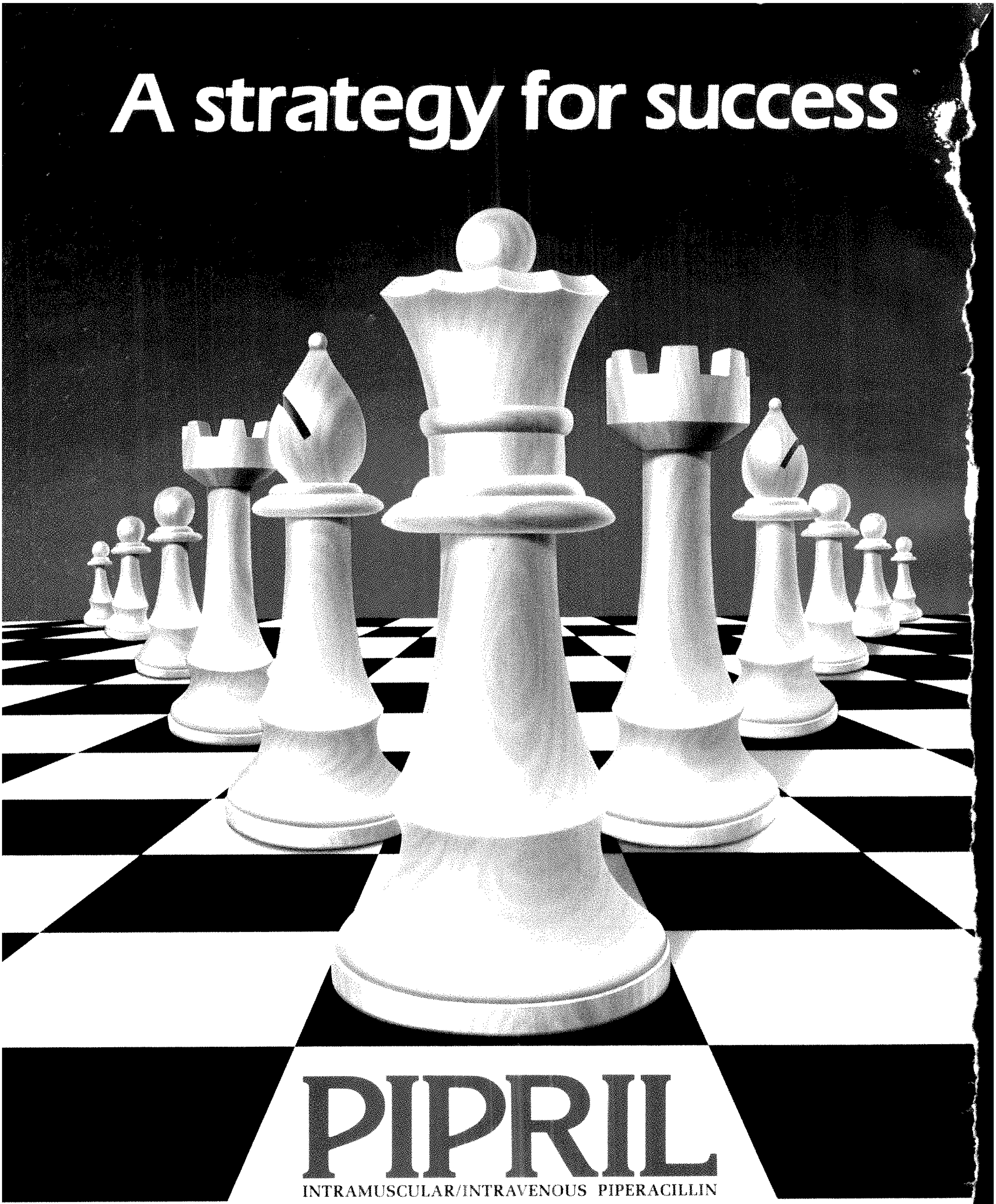

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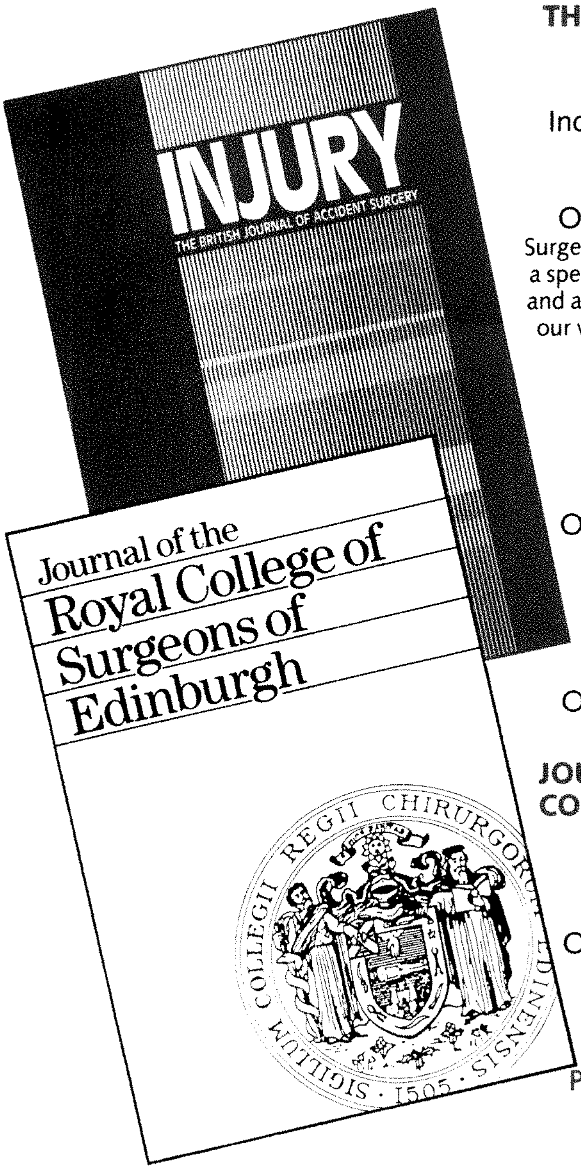
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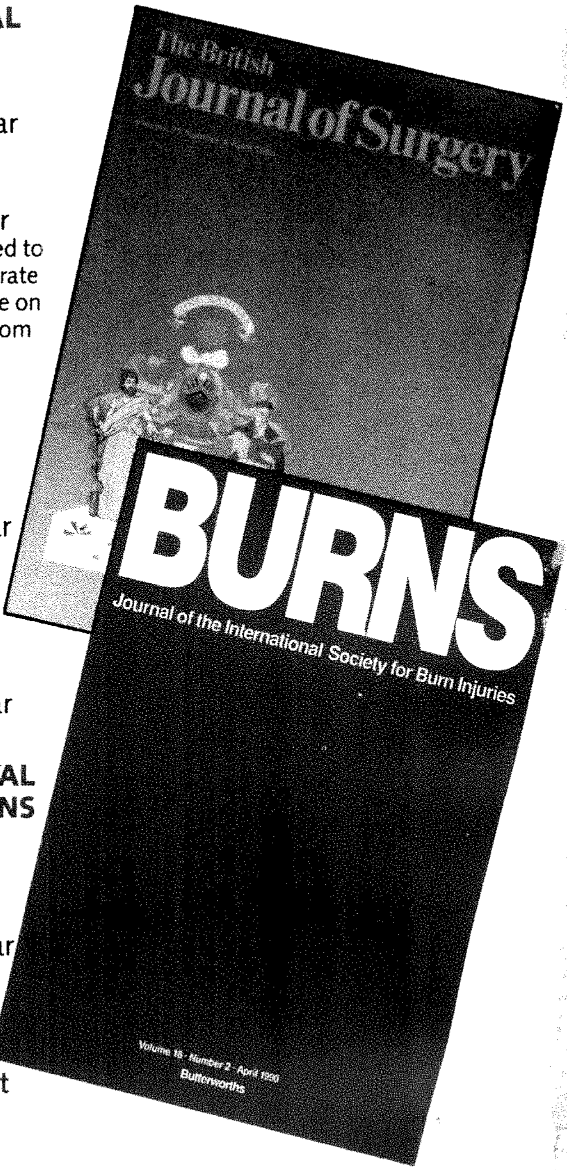
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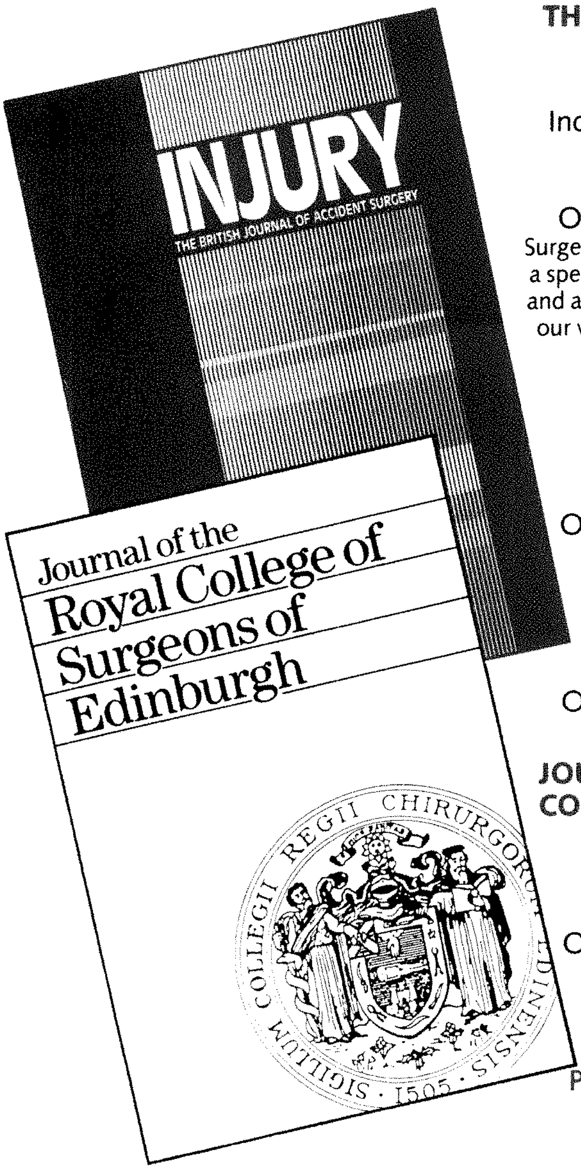
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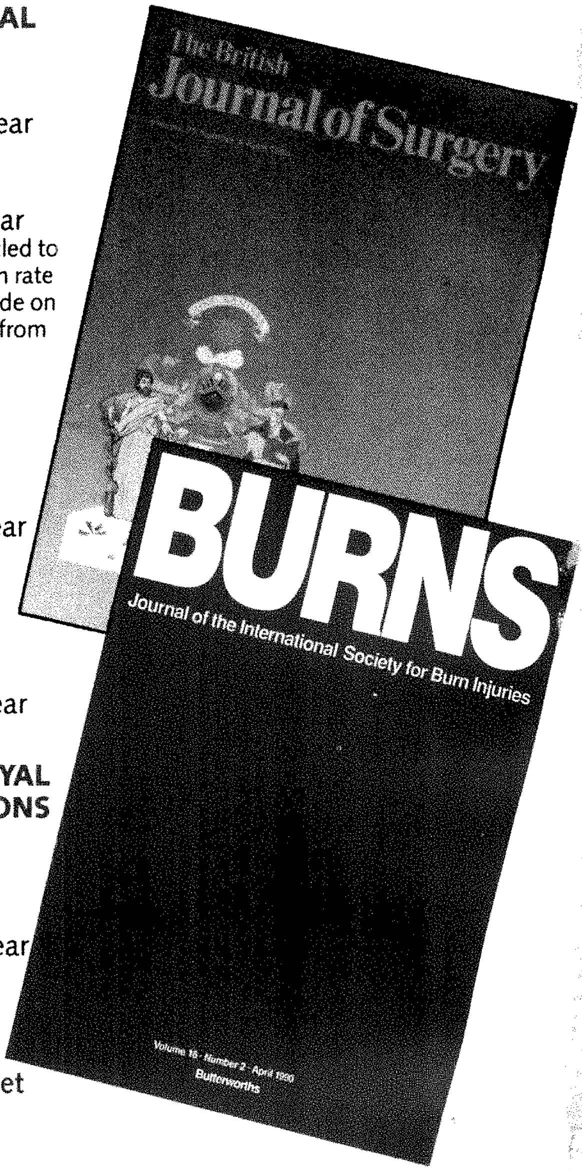
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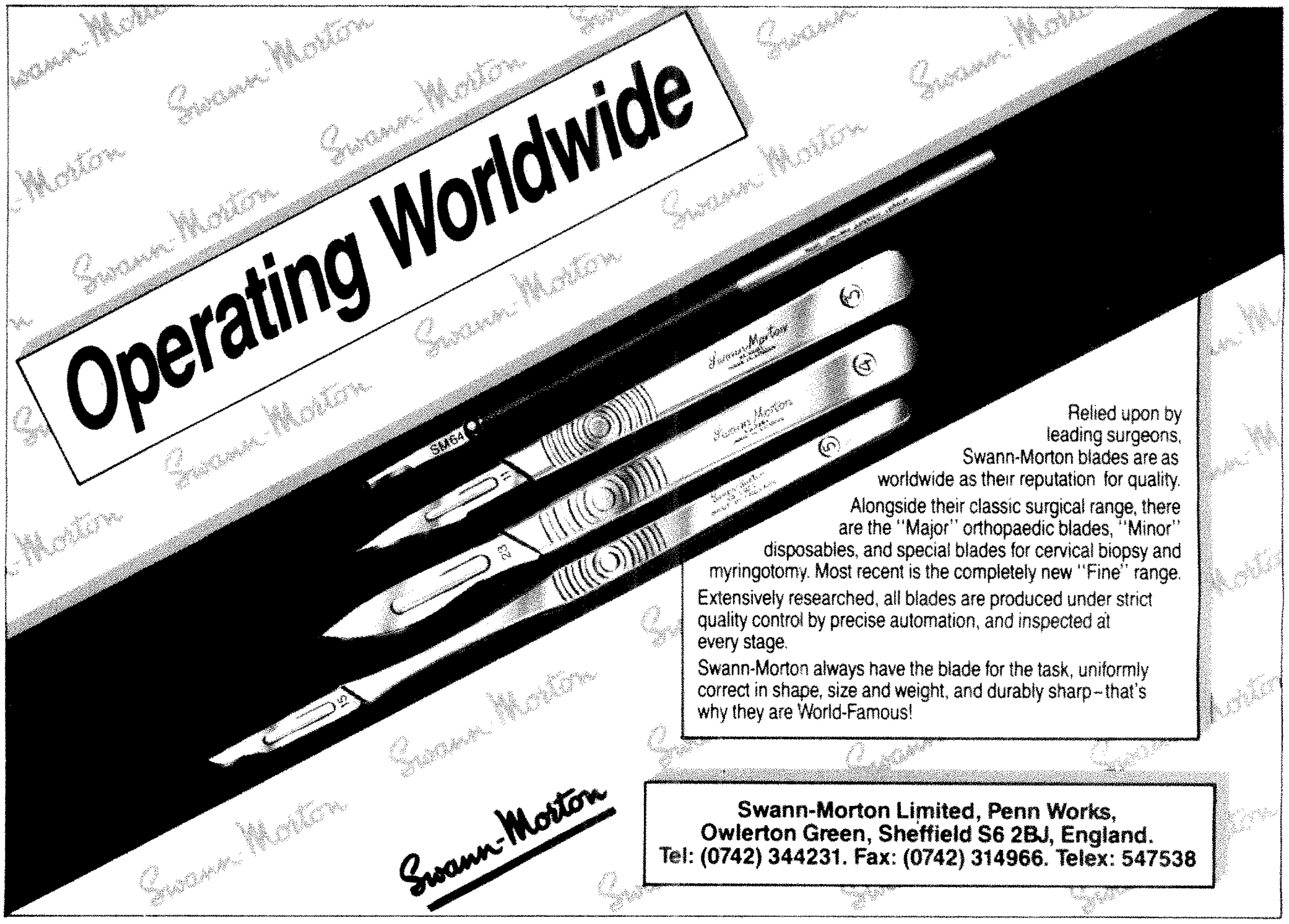

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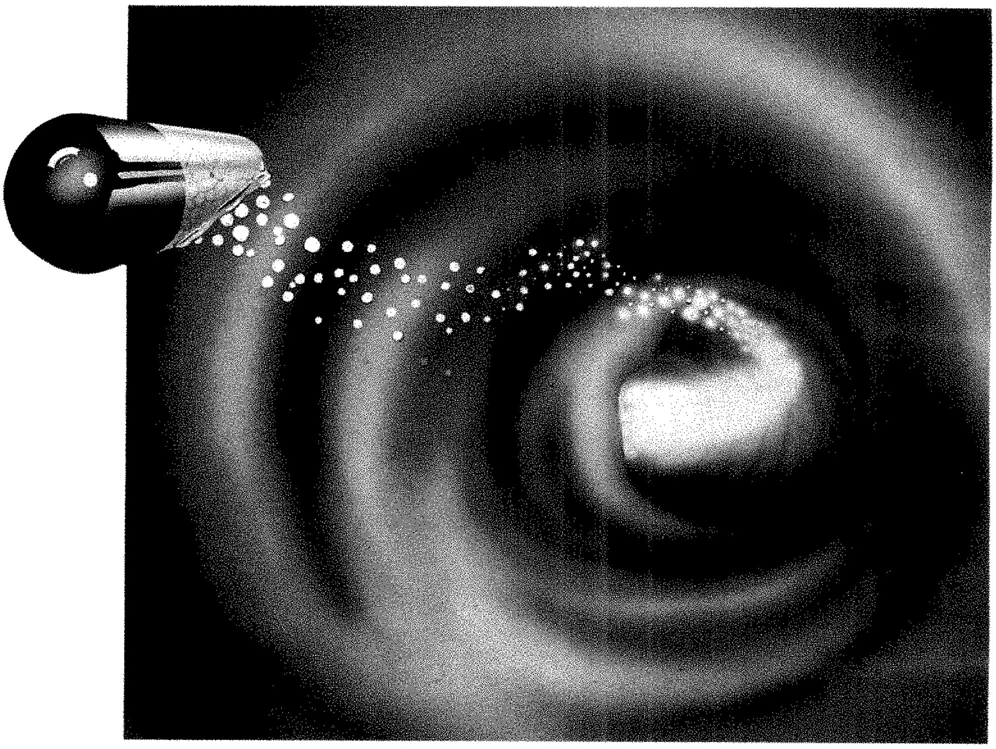

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Minimally invasive surgery

In the late 1970s and early 1980s an entirely new attitude began to appear within some branches of surgery which opened the path for minimally invasive surgery. This change is best illustrated in the history of renal stone surgery where the development of percutaneous stone removal at the Institute of Urology in London[1] and the University of Mainz in Germany[2] ensured that the trauma of surgical access was reduced to a minimum. New endoscopic instruments were produced giving the urologist an excellent view of the interior of the kidney and thereby decreasing the time spent operating while ensuring that stones could be satisfactorily removed and that postoperative complications were minimized.

Eventually, in 1980, the treatment of urinary calculi by extracorporeal shockwave lithotripsy (ESWL) was reported[3]. This was an entirely new concept whereby an electrical discharge from outside the body could fragment calculi within the urinary tract. This ensured that the physical trauma inflicted upon the patient was reduced to a minimum while achieving a maximum therapeutic result. Although the various methods for treating urinary calculi have never been submitted to a clinical trial, ESWL does seem to be the most satisfactory method of treating stones of 3 cm or less in diameter. In the case of staghorn calculi, a combination of percutaneous debulking and ESWL is preferable. Thus the removal of most renal stones has been transformed from an aggressive, debilitating operation necessitating prolonged hospitalization and convalescence to an out-patient procedure.

Minimally invasive procedures may be carried out through natural tracks or tracks prepared by the interventional radiologist or surgeon. A philosophical leap was required in the acceptance of prepared tracks for minimally invasive surgery, but such procedures have now been performed for many years. For example, Wittmoser introduced transthoracic endoscopic sympathectomy in the 1950s[4], Burhenne has extracted residual stones percutaneously from the common bile duct through the T tube tract since 1972[5], and Fernstrom carried out the first percutaneous removal of a renal stone in 1976[6]. In spite of this, it is interesting that some surgeons initially preferred open renal stone removal through a lumbotomy incision, and mini-cholecystlithotomy through a small abdominal incision, to the less invasive and technically easier percutaneous procedures. Percutaneous endoscopic resection of upper urinary tract transitional cell tumours has been performed[7], and how far away are we from percutaneous aspiration of a renal cell carcinoma following ultrasonic destruction of the tumour with the Cavitron (C.U.S.A.®, Valleylab, London, UK)

Arthroscopy is now accepted as the method of choice for the management of tears of the menisci in the knee. It has also been used to examine many joints, including the wrist, elbow, shoulder and ankle. Percutaneous discectomy is currently under evaluation and appears to be extremely useful in selected cases. It is surely not beyond the bounds of possibility that, in future, percutaneous hip replacement may be performed.

Great interest has also been shown in the fragmentation of gallstones by ESWL[8]. The results have been encouraging, but the technique is limited by the requirement that the gallbladder must be functioning and that best results are obtained if ESWL is followed by prolonged administration of bile acids. Percutaneous cholecystlithotomy and cholecystlithotripsy[9] have been suggested as an adjunct to ESWL, but they may also be performed as independent procedures with a high success rate and a low incidence of complications.

Dubois and colleagues[10] have performed 250 laparoscopic cholecystectomies with excellent results and in some cases this may be performed as a day case under local anaesthesia. Under laparoscopic vision, the view of the gallbladder is exactly the same as if the abdomen were laid open before the operating surgeon. Through two separate stab incisions other instruments are introduced. The approach to the cystic duct and cystic artery is magnified, and the gallbladder can be dissected from the liver with endoscissors and diathermy. A cannula can be inserted into the common bile duct to perform a cholangiogram; if a stone is seen a flexible ureteroscope may be inserted through the cystic duct stump and the stone broken up under direct vision using the laser.

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The transthoracic endoscopic approach to the sympathetic chain is well known and widely used. Transanal resection of rectal tumours located up to 20 cm from the anal verge with full thickness excision of the rectal wall and end-to-end anastomosis has also been performed. Instead of the blind approach to the thoracic oesophagus in transhiatal oesophagectomy, the thoracic dissection can now be performed under endoscopic control with accurate diathermy of individual vessels.

Semm[11] has performed many gynaecological techniques through the laparoscope including removal of the adnexae, excision of ovarian cysts, myomectomy, management of tubal pregnancies, and tubal ligation. He has introduced laparoscopic techniques for tying ligatures around structures and has been the leader in the introduction of laparoscopic appendicectomy. It is an indication of the interdisciplinary nature of minimally invasive surgery that gynaecologists are now using the transurethral resectoscope to resect the endometrium under local anaesthesia as an alternative to hysterectomy in selected cases.

In December 1989 the inaugural meeting of the Society of Minimally Invasive Therapy was held at the Royal Institution in London. The aims of the Society are to include: development of a closer cooperation between clinicians and manufacturers in research and development; to present papers which offer practical help to those embarking on minimally invasive surgery; and to introduce courses throughout the world instructing surgeons in the various minimally invasive techniques.

The era of minimally invasive therapy has begun. It is likely that percutaneous removal of organs will become commonplace and that percutaneous reconstructive procedures will become possible. New instruments will be made which will facilitate and accelerate these procedures. New imaging techniques will provide a clear view of the internal organs while therapeutic procedures are performed. It is essential that we as surgeons grasp the opportunity provided by the new minimally invasive techniques but, unhappily, many areas have been taken over by the interventional radiologists. This is entirely our own fault for not adopting the new instrumental techniques that are rapidly becoming available. It is important to appreciate that these concepts are beginning to cause a different approach to various common operative procedures. We must begin to appreciate the advantages afforded to the patient by minimally invasive techniques and turn our minds to minimizing trauma while still achieving our therapeutic aims.

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Clinical relevance of sphincter of Oddi dysfunction

The sphincter of Oddi is a small smooth muscle sphincter which is situated at the junction of the terminal bile duct, pancreatic duct and duodenum. As a result of its strategic position at one of the busiest junctions in the gastrointestinal tract, it is not surprising that disordered function of the sphincter may be associated with clinically relevant symptoms. During the last decade a number of studies have been conducted in order to help understanding of the sphincter's function, identify dysfunction and propose treatment.

The 'functional' studies carried out in man show that the sphincter of Oddi is characterized by phasic contractions which are superimposed on a modest basal pressure (tone). These phasic contractions are present at all times and throughout all cycles of the interdigestive motor activity. The contractions propel small volumes of fluid from within the ducts into the duodenum; however, along with the basal pressure, they provide a small resistance to flow across the choledocho and pancreaticoduodenal junction. After a meal the contractions are inhibited but not abolished, the basal pressure is reduced and these effects reduce the resistance in order to promote flow[1]. Control of this activity is thought to be via an interplay of neuronal as well as hormonal reflexes[2]. Recent studies show that increase in intraluminal pressure within the proximal biliary tract and gallbladder reduces resistance to flow across the sphincter[3].

Dysfunction of the sphincter of Oddi as a clinical entity becomes evident in patients who have had a cholecystectomy. This does not necessarily mean that the problem was not present prior to cholecystectomy. However, in patients with an intact biliary tract, the gallbladder may dampen the effects of alteration in pressure produced by sphincter of Oddi motility changes and hence its removal brings to light any underlying problem. There is a suggestion that at least in some patients sphincter of Oddi dysfunction may be produced by injury to important nerves of the sphincter or follow instrumental injury to the sphincter of Oddi[3]. In the majority of patients, however, the cause of sphincter of Oddi dysfunction is unknown.

Sphincter of Oddi dysfunction is present in a small percentage of patients who complain of severe upper abdominal pain, usually 5 to 10 years after cholecystectomy. In some of these patients the pain may be associated with abnormal elevation of serum liver enzymes, or a dilated bile duct and delayed emptying of contrast medium introduced into the bile duct at endoscopic cholangiography. A separate group of patients may present with pain consistent with pancreatitis and estimation of serum amylase shows it to be abnormally elevated. In neither group of patients can common causes of biliary or pancreatic pain such as stones, stricture or alcohol be implicated and in the past the label of either 'idiopathic' or 'functional' upset was given to these patients.

Non-invasive investigations such as the morphine–neostigmine test, fatty meal sonography of the bile duct, secretin stimulated estimation of pancreatic duct diameter or radionuclide estimation of bile flow may be used to support the hypothesis that the pain may originate at the sphincter of Oddi. However, the most objective investigation that is available for the diagnosis of this disorder is that of endoscopic sphincter of Oddi manometry. Based on findings at endoscopic sphincter of Oddi manometry[4], sphincter of Oddi dysfunction is categorized into two major groups:

Stenosis of the sphincter of Oddi

Manometrically this group of patients is characterized by an abnormally elevated sphincter of Oddi basal pressure. The stenosis may be due to fibrotic changes in the sphincter or smooth muscle hyperplasia. However to date, strong pathological correlation does not exist.

A recently completed prospective study has shown that most patients with the stenotic pattern on manometry are cured of their biliary-like pain following endoscopic division of the sphincter[5]. Similarly, in patients with idiopathic recurrent pancreatitis and a manometrically demonstrated stenosis of the sphincter, surgical sphincteroplasty and pancreatic duct septectomy is associated with a high success rate in the relief of symptoms[6].

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Sphincter of Oddi dyskinesia

This group of patients has a variety of findings on manometry which at this stage have been grouped under the heading of dyskinesia. With further understanding of sphincter of Oddi motility disorders, the groupings may become inappropriate.

(a) *Rapid phasic contraction frequency.* Spontaneously occurring bursts of rapid contraction may be seen and are thought to reflect an 'irritable' sphincter. The rapid contractions may produce transient obstruction to flow.

(b) *Intermittent episodes of elevated basal pressure.* This is similar to the abnormality present in the group above and may be an associated finding. The manometric finding may also reflect an 'irritable' sphincter which goes into 'spasm' intermittently.

(c) *Excessive retrograde contractions.* In normal subjects the majority of sphincter of Oddi contractions are oriented in an antegrade direction. However, in some patients a majority of retrograde contractions are found. This finding is also seen in patients with gallbladder and common bile duct stones and may result in a relative retardation to flow through the sphincter.

(d) *Paradoxical response to cholecystokinin.* Administration of a bolus dose of cholecystokinin octapeptide normally results in inhibition of sphincter of Oddi phasic contractions[7]. This action is thought to be mediated via an effect on non-adrenergic non-cholinergic nerves to the sphincter of Oddi[8]. A paradoxical response consists of sphincter contraction instead of inhibition, and may be due to a direct effect of the hormone to the sphincter. The finding may reflect damage to the intrinsic neurones of the sphincter of Oddi and may be a condition pathologically similar to that seen in achalasia of the oesophagus.

The data accumulated so far lead us to conclude that sphincter of Oddi dysfunction is a clinically relevant condition. It is by no means definitively categorized and the aetiological factors are not clearly defined. However, via the agency of sphincter of Oddi manometry, a distinct group of patients can be defined with a manometric abnormality. Those patients with biliary type pain and a manometrically defined stenosis respond well to division of the choledochal sphincter by endoscopic sphincterotomy. Similarly patients with idiopathic recurrent pancreatitis and a manometrically recorded stenosis of the pancreatic sphincter respond to total division of the sphincter by an operative sphincteroplasty and pancreatic duct septectomy. Effective treatment for patients with the other manometric abnormalities (i.e. the dyskinetic group) has not been determined yet, and awaits the results of further studies.

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Tamoxifen therapy in unresectable adenocarcinoma of the pancreas and the papilla of Vater

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Between 1984 and 1987, 176 Norwegian patients with histologically verified unresectable pancreatic adenocarcinoma were randomized to double-blind treatment with oral tamoxifen (30 mg daily; 48 men and 44 women) or placebo (47 men and 37 women). Analysis of oestrogen receptor activity in the carcinomas was not performed. There were no statistically significant differences between the two groups according to age, Karnofsky performance index, tumour node metastasis (TNM) stage, operative treatment or other patient characteristics. The tamoxifen or placebo treatment continued to death or to 10 months after accrual into the trial was stopped. In the tamoxifen group, the mean and median survivals were 205 and 115 days, respectively. These values did not differ statistically from the 192 and 122 days, respectively, observed in the placebo group. Additional retrospective analyses of sex and stage revealed no beneficial effect of tamoxifen upon survival. For women in stage III (any T N1 M0), mean and median survivals were 255 and 191 days, respectively, compared with values of 84 and 45 days, respectively, in the placebo group (P = 0·011). After 2·5 years, three (7 per cent) women in the tamoxifen group were still alive compared with no survivors in the placebo group. No male patients survived beyond 2·5 years. This therapeutic result in a small subgroup of women is probably incidental and not an effect of tamoxifen.

Keywords: Pancreas, adenocarcinoma, unresectable, tamoxifen, randomized, double-blind, trial

Despite considerable sophistication of diagnostic techniques, 'early' detection of pancreatic carcinoma is still rare. About 80 per cent of Norwegian patients have advanced regional disease or distant spread at the time of primary diagnosis and treatment[1]. The treatment results are poor, with a 1-year survival rate slightly above 10 per cent[1]. Even if curative surgical resection is possible, the 5-year survival rate is only 3–13 per cent[2–8]. Treatment with radiation and/or cytotoxic drugs in patients with unresectable carcinoma does not improve long-term survival in most reports[9–14]. However, Mallinson *et al.*[15] showed significantly improved survival in patients with unresectable pancreatic carcinoma treated with combination chemotherapy and Dobelbower[16] and Dobelbower and Milligan[17] have shown that radiotherapy can provide long-term survival rates in unresectable carcinoma that are as high as those achieved by curative resection alone.

Some intriguing data suggest that sex steroid hormones are involved in the development of exocrine pancreatic carcinoma. Firstly, there is an excess incidence of pancreatic cancer in men aged less than 50 years, whereas the male:female incidence ratio decreases with age and approaches unity above the age of 70 years[18,19] Secondly, a higher incidence of ovarian stromal and endometrial hyperplasia is present post-mortem in women with pancreatic carcinoma, which suggests excessive sex hormone activity in this malignancy[20]. Thirdly, prior oophorectomy, spontaneous abortion and uterine myomatous change are significantly commoner in women with cancer of the pancreas than in controls[21]. In addition, previously oophorectomized patients develop pancreatic cancer at a substantially earlier age Finally, the growth of a transplanted ductular pancreatic carcinoma cell line in hamster cheek pouches is reduced by oestrogen treatment[22].

Oestrogens could influence the development of pancreatic carcinoma by binding to intracellular receptors or to specific oestrogen binding proteins. In fact, oestrogen receptor activity and/or specific oestrogen binding proteins have been demonstrated in pancreatic carcinoma as well as in normal pancreatic tissue by five different research groups[23–27].

In mice, the antioestrogenic drug tamoxifen accumulates to a higher extent in the pancreas than in established oestrogen target organs such as the mammary gland and uterus[28]. Tamoxifen has been shown to increase the survival of patients with unresectable pancreatic carcinoma in two small uncontrolled studies[29,30] whereas another study demonstrated no such response[31] The present study examines the potential value of tamoxifen in a controlled study of 176 patients with unresectable pancreatic cancer

Patients and methods

Thirty-eight Norwegian hospitals participated in the present trial In all, 472 patients with pancreatic cancer were entered into the trial between April 1984 and April 1987 Radical resection was performed in 108 patients during this period One patient had a second-look operation Data regarding the case history, diagnosis and resectability assessment, macroscopic and microscopic examinations, surgical procedure and postoperative follow-up were recorded on standardized forms which were regularly submitted to the study headquarters for computation

The Norwegian Pancreatic Cancer Trial comprises two randomized studies (1) a study to evaluate the effect on survival of adjuvant chemotherapy (5-fluorouracil, Adriamycin® (Farmitalia Carlo Erba, Milan, Italy) and mitomycin C, modified FAM) after radical resection *versus* surgery alone Patient accrual in this study is still in progress and the trial will not be discussed further, and (2) an investigation to elucidate the effect of oral tamoxifen *versus* placebo on survival in patients with advanced unresectable pancreatic carcinoma Twenty-seven hospitals entered patients into the study, which forms the basis of the present report.

Eligibility for the trial

Only patients with histologically or cytologically verified adenocarcinoma of the exocrine pancreas or the papilla of Vater were included

This study was written on behalf of the Norwegian Pancreatic Cancer Trial K. E Bakkevold is trial co-ordinator and Fellow of the Norwegian Cancer Society

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in the trial. Patients with pancreatic tumour and liver metastasis who had not been operated on were included after histological or cytological verification of the metastasis

Patients with endocrine tumour, cholangiocarcinoma, metastatic pancreatic tumour, cystadenocarcinoma and histologically or cytologically unverified primary pancreatic tumour were excluded.

Selection of patients

Eligible patients with non-resectable primary tumours or regional lymph node metastasis not removable *en bloc* with the primary tumour (as judged by operative assessment) or patients with distant metastasis were included in the study. Oestrogen receptor analysis on material from the primary tumour or metastasis was not performed and receptor status was not used as a criterion for inclusion or stratification.

Exclusion criteria

Exclusion criteria were age above 75 years, Karnofsky index below 60, previous radical resection for pancreatic cancer, previous chemotherapy or radiotherapy for malignant disease, concomitant separate malignant disease or current receipt of hormonal therapy or tamoxifen.

Randomization

Randomization was undertaken by using a table of random numbers in blocks of ten patients. Five patients in each block received tamoxifen and five received placebo. Each participating hospital was supplied with a sufficient number of blocks corresponding to the expected number of patients The prepacked tablets (ten tablet packs in each block) were marked with a five-digit number which was used as the personal registration number for each patient and used on all the treatment and follow-up forms

Patients who fulfilled the entry criteria were randomized shortly before hospital discharge and after written informed consent. Randomization was performed by Haukeland University Hospital Pharmacy and a tablet pack containing 3 months' tablet supply was marked with the name and registration number and sent to the patient via the local doctor. Identical tablet packs were supplied via the local doctor every third month All patient codes were kept secret by the pharmacy and could be broken only in case of emergency. Thus the randomization process and coding was completely blinded for the patients, the local doctors, the study chairman and the headquarters staff The tamoxifen and placebo tablets were indistinguishable both in appearance and taste

Therapy

Nolvadex® (ICI, Macclesfield, UK) 10 mg tablets (dose 30 mg tamoxifen daily) or placebo tablets of identical appearance were taken in the morning Treatment was given on an outpatient basis until the patient wished to discontinue medication or could no longer tolerate the tablets. If there was proven considerable disease progression, medication could be discontinued and palliative radiation or cytotoxic therapy was instituted without withdrawal from the study

Study design and statistical methods

The therapeutic goal was to increase median survival from 6 months to 9, 10 or 12 months. Group size estimation was based on this goal. Using $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}10$, 222, 146 and 86 patients, respectively, were needed to detect such differences. Treatment duration was calculated from the day of randomization to either the death of the patient or the end of follow-up, in patients included in the later stages of the trial treatment continued to 10 months after accrual to the study had ended

Non-censored variables were compared by χ^2 analysis, survival time was described by Kaplan–Meier plots[32] Survival in the two groups was compared by the log rank test[33]. Using a two-tailed test, a P value $<0{\cdot}05$ was regarded as statistically significant. All randomized patients, withdrawals included or excluded, were analysed In addition, the entire material was retrospectively (after randomization) stratified according to sex, stage of disease, and surgery or no surgery These subgroups were also analysed including and excluding withdrawn patients The computations were performed using the BMDP (BMDP Statistical Software, Los Angeles, California, USA) statistical program package implemented on the Univac 1100 (Sperry Univac, Salt Lake City, Utah, USA) computer of the University of Bergen

Staging

The tumour node metastasis (TNM) clinical classification for carcinoma of the pancreas or the papilla of Vater was used[34]. The classification criteria as well as stage grouping (I–IV) are shown in *Table 1*

Ethical considerations

Written informed consent was obtained from all patients The regional official ethics committee of Western Norway approved the trial

Patient characteristics

Clinical characteristics of patients included and of patients excluded before randomization are presented in *Table 2*

Table 1 *TNM clinical classification of included patients with carcinoma of the pancreas or papilla of Vater*

Stage	Pancreas	Papilla of Vater
T (Primary tumour)		
T0	No evidence of primary tumour	–
T1	Tumour limited to pancreas T1a. tumour ⩽2 cm in its greatest dimension T1b. tumour >2 cm in its greatest dimension	Tumour limited to the papilla T1a and T1b. as for pancreas
T2	Tumours extending beyond confines of pancreas involving one or more of the duodenum, bile duct, peripancreatic fat and/or nerves	Tumour extending beyond confines of papilla involving one or more of the duodenum, bile duct or pancreas
T3	Tumours extending beyond confines of pancreas involving one or more of the stomach, spleen, colon or adjacent large vessels	Tumour extending beyond confines of papilla involving one or more of the stomach, colon or adjacent large vessels
TX	Minimum requirements to assess primary tumour cannot be met	As for pancreas
N (Lymph nodes)		
N0	No evidence of regional lymph node involvement	As for pancreas
N1	Evidence of involvement of regional lymph nodes related to primary tumour	As for pancreas
NX	Minimum requirements to assess regional lymph nodes cannot be met	As for pancreas
M (Distant metastasis)		
M0	No evidence of distant metastasis	
M1	Evidence of distant metastasis	
MX	Minimum requirements to assess presence of distant metastasis cannot be met	

Stage grouping			
Stage I	T1 T2	N0	M0
Stage II	T3	N0	M0
Stage III	Any T	N1	M0
Stage IV	Any T	Any N	M1

Table 2 *Characteristics of patients*

	Tamoxifen group (*n*=92)	Placebo group (*n*=84)	*P**	Excluded patients (*n*=187)
Age (years)				
Mean(s.e.m.)	64·3(0·8)	65·5(0·9)		71·8(0·8)
95 per cent confidence interval	62·7–65·9	63·7–67·3		70·2–73·3
Median(s.e.)	66·0(0·9)	66·0(0·9)	0·82	75·0(1·2)
Karnofsky index				
Mean(s.e.m.)	76·7(1·5)	77·8(1·4)		63·2(1·6)
95 per cent confidence interval	73·6–79·7	75·0–80·6		60·1–66·3
Median(s.e.)	80·0(2·9)	80·0(2·9)	0·92	60·0(2·9)
Diagnostic delay (days)†				
Mean(s.e.m.)	133·4(20·7)	113·8(9·7)		125·7(12·1)
95 per cent confidence interval	92·4–174·5	94·4–133·2		101·8–149·6
Median(s.e.)	89·0(5·5)	91·5(12·7)	0·30	71·0(9·0)
s-bilirubin before operation (μmol/l)				
Mean(s.e.m.)	90·0(11·4)	88·9(12·9)		121·7(11·7)
95 per cent confidence interval	67·3–112·8	63·2–114·7		98·6–144·8
Median(s.e.)	61·0(26·6)	30·5(21·4)	0·21	72·0(26·0)
Sex				
No. of men	48(52)	47(56)		89(48)
No. of women	44(48)	37(44)	0·73	98(52)
Tumour site				
Papilla	1(1)	2(3)		5(4)
Head	46(68)	48(74)		98(74)
Body	19(28)	12(18)		28(21)
Tail	2(3)	3(5)		2(1)
Total	68(100)	65(100)	0·55	133(100)
Incomplete data	24	19		54
TNM stage				
I (T1T2N0M0)	2(2)	2(2)		7(4)
II (T3N0M0)	12(13)	13(15)		18(10)
III (Any T N1M0)	17(18)	16(19)		21(11)
IV (Any T Any N M1)	51(55)	43(51)		99(53)
I–II (T1–T3N0M0)	0(0)	0(0)		1(1)
I–III (TXNXM0)	0(0)	2(2)		9(5)
I–IV (TXNXMX)	1(1)	1(1)		16(9)
II–III (T3NXM0)	8(9)	7(8)		14(7)
II–IV (T3NXMX)	1(1)	0(0)	0·84	2(1)
Preoperative biliary drainage				
Endoscopic	8(10)	6(8)		16(10)
Percutaneous transhepatic	4(5)	6(8)		25(15)
None	72(86)	66(85)	0·70	126(75)
Incomplete data	8	6		20
Surgical procedure				
Whipple's operation	2(3)	2(3)		1(1)
Exploratory laparotomy	15 (23)	14(23)		30(24)
Biliodigestive anastomosis	29(44)	29(47)		49(39)
Biliodigestive anastomosis + gastroenterostomy	20(30)	17(27)		46(37)
Incomplete data	3	5	0·98	10
Surgical details				
No. operated on	66(74)	62(78)		126(71)
No. not operated on	23(26)	17(22)		51(29)
No. with complications after surgery (not fatal)	9(14)	12(19)		36(30)
No. without complications	56(86)	51(81)		85(70)
Incomplete data or not operated on	27	21	0·43	66

Values in parentheses are percentages unless otherwise stated; * χ^2 analysis between tamoxifen and placebo groups; † time in days between onset of symptoms and diagnosis

Withdrawals (Table 3)

The survival analyses were performed both including and excluding withdrawn patients.

Evaluation of outcome and follow-up

After hospital discharge all patients were followed at the local outpatient clinic every third month for 2 years and then every sixth month for up to 5 years or until disease progression prohibited further outpatient visits. Evaluation included clinical examination and estimation of the Karnofsky index and registration of postoperative complications, compliance, adverse effects of therapy and survival. The follow-up results were registered on standardized record forms and submitted to the study headquarters. Further information concerning survival was obtained via the Cancer Registry of Norway in Oslo, Norway. Three months after hospital discharge 60 patients (56 per cent of all randomized patients still being alive) were adequately followed up. This figure diminished to 40 per cent after 12 months and to 14 per cent after 2 years.

Compliance

At each follow-up visit patient compliance was estimated by counting the number of unused tablets.

Table 3 *Withdrawal of patients after randomization*

	No of patients	
	Tamoxifen	Placebo
Unwillingness to comply with treatment for at least 6 weeks	1	–
Violation of entry criteria		
A malignancy other than pancreatic carcinoma	–	1
Age over 75 years	1	3
Karnofsky index below 60	6	2
Radically resected with free margin	1	1
Radically resected without free margin	1	1
Total	10	8

Table 4 *Reasons for exclusion of patients before randomization*

	No of patients ($n=187$)
Patients older than 75 years and/or Karnofsky index below 60	140
Postoperative death	16
Unwillingness	7
Other concomitant type of malignant disease	1
Patients receiving therapy with tamoxifen	2
Autopsy diagnosis	3
Patients receiving cytotoxic chemotherapy	15
Unknown	3

Table 5 *Time between operation and randomization for surgically treated patients and between diagnosis and randomization for non-surgically treated patients*

Patient group	Mean no of days	95% confidence interval	Median no of days
Operated on			
Tamoxifen	13·9(1·3)	11·3–16·5	13·0(1·2)
Placebo	16·0(1·8)	12·3–19·6	13·5(1·2)
Not operated on			
Tamoxifen	20·1(3·5)	12·9–27·2	19·5(4·0)
Placebo	20·8(3·8)	12·8–28·7	15·0(4·0)

Values in parentheses are standard errors

Results

In the present Norwegian trial patients with unresectable, histologically proven pancreatic carcinoma were accrued between April 1984 and April 1987. In all, 177 fulfilled the inclusion criteria and were randomized to receive tamoxifen or placebo. One patient had incorrectly been randomized twice and was excluded. A total of 187 patients was excluded before randomization. Characteristics of included and excluded patients are presented in *Table 2*. Statistically, these characteristics were equally distributed between the tamoxifen and placebo groups. In the same period, 107 patients were radically resected and were eligible only for the FAM study. One patient had a second-look operation.

The reasons for patient exclusion before randomization are given in *Table 4*. Eighteen of the excluded patients were eligible. Among these 15 received chemotherapy but there is no information about survival in this group.

Eighteen patients were withdrawn from the study after randomization (*Table 3*), one in accord with criteria stated in the trial protocol and 17 because they were not eligible. Survival analyses were performed for all randomized patients irrespective of the eligibility criteria.

According to the protocol, randomization should have been performed before hospital discharge. The time interval between operation and randomization is shown in *Table 5*. Three patients randomized before surgery had to be excluded. The survival time was calculated fom the day of randomization to death or for censored patients to 16 March 1988, when the survival analyses were performed. Survival data were partly based on information via the Cancer Registry of Norway, including all cancer deaths until 31 December 1987.

Survival

For the patients randomized to tamoxifen treatment, mean and median survivals were 205 and 115 days, respectively, compared with values of 192 and 122 days in the placebo group. The difference was not statistically significant ($P=0·731$, power$=0·816$). A similar analysis of the two groups after exclusion of the withdrawn patients revealed no difference ($P=0·81$, power$=0·782$). *Figures 1–3* demonstrate the life table analyses and the overall survival for all randomized patients and for the two sexes. With one exception there was no survival difference when comparing sex, stage or surgery/no surgery with matched placebo groups. The exception comprised female patients in stage III. They had mean and median survivals of 255 and 191 days, respectively, in the tamoxifen group and 84 and 45 days in the placebo group ($P=0·011$). An analysis of all randomized women, however, revealed no survival difference ($P=0·8549$, power$=0·261$).

The survival of those patients who were alive after 60, 90, 100, 150, 365, 550 and 730 days in both groups was also calculated to look for a delayed treatment effect. No treatment effect could be discerned when analysing the whole group or when examining either sex independently.

Long-term survival

Eight patients in the tamoxifen group and seven in the placebo group survived for more than 1 year. In the tamoxifen group, seven of the women (16 per cent) survived for more than 1 year and two (5 per cent) are still alive after 3 years. There were no survivors beyond 2·5 years in the placebo group (*Table 6*).

Adverse reactions

Three patients in the tamoxifen group had mild adverse reactions; none was fatal. One woman developed hirsutism, one a vaginal discharge and one, who had liver metastases, displayed a hepatotoxic reaction which subsided after stopping the drug. There were no adverse reactions in men or in the placebo group.

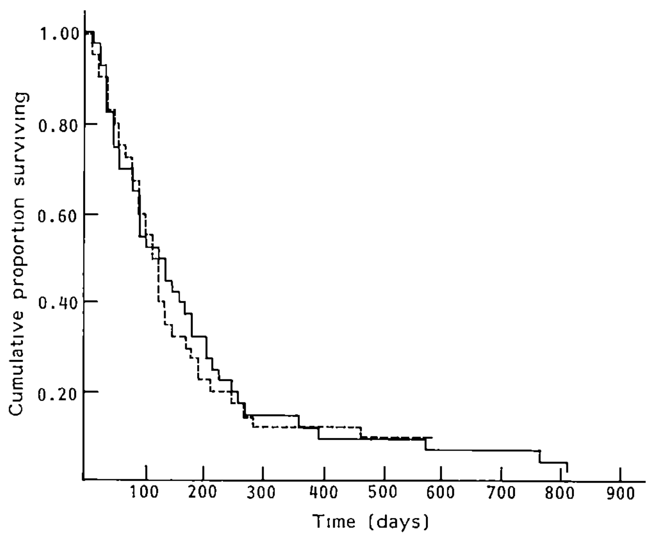

Figure 1 *Life table analysis of total survival for all randomized patients, log rank test* P=0·7312, *power=0·816,* (----), *tamoxifen group,* (——), *placebo group*

Quality of life

After 3 months' follow-up, 60 per cent of the patients were at home; 32 per cent had a feeling of improvement, 49 per cent felt worse and 18 per cent were unchanged. Fifty-seven per cent had severe pain or pain of moderate severity requiring analgesics; 28 per cent complained of nausea or vomiting and 25 per cent had diarrhoea/steatorrhoea. Their functional condition as judged by the Karnofsky index was 60 or lower in 50 per cent of the patients. As measured by the above parameters, the quality of life after 3, 6 and 9 months in both groups was compared using χ^2 analysis. There were no differences between the groups.

Discussion

Selection of patients for the present trial was performed at each participating hospital in accord with a trial protocol without any stratification. This was done because firm conclusions with regard to influential prognostic factors can hardly be drawn beforehand. TNM staging[34] was performed retrospectively during the last 6 months of the patient accrual period, but before the analyses were started. In spite of this, the tamoxifen and placebo groups seemed to be well balanced and without any statistically significant differences (*Table 2*)

There was no effect of tamoxifen upon survival. The median survival time of 115 days observed in the tamoxifen-treated patients was shorter than the 8·5 and 7 months found in the small non-randomized studies by Theve *et al.*[29] and Tønnesen *et al.*[30]. They used historical control groups in which median survival was 2·5 and 3 months, respectively. The difference between the results of their studies and the present one clearly demonstrates the value of properly balanced, doubly blinded, randomized trials involving a sufficient number of patients.

Seven of the patients in the placebo group were still alive 1 year after randomization and four of them even after 2 years. Crowson *et al.*[31] treated 14 patients with tamoxifen. They started with a loading dose of 160 mg followed by a maintenance dose of 40 mg daily. They found no response at all. Only one patient survived for more than 6 months. The comparatively poor prognosis observed in their study may be explained by differences in the patient population.

Wong *et al.*[35], in an uncontrolled study, treated 24 patients with 40 mg tamoxifen daily and found an overall median survival of 7 months. Corresponding figures for the female and male subgroups were 10 and 4 months, respectively Six women in their study survived for more than 1 year and three for more than 2 years. They suggest that a subgroup of patients with unresectable ductal adenocarcinoma of the pancreas may have a survival benefit from tamoxifen treatment and that this benefit is confined to postmenopausal women. We found a statistically significant tamoxifen effect in women in stage III. In our trial, however, the patients were not stratified into sex and stage subgroups before randomization. Although there were

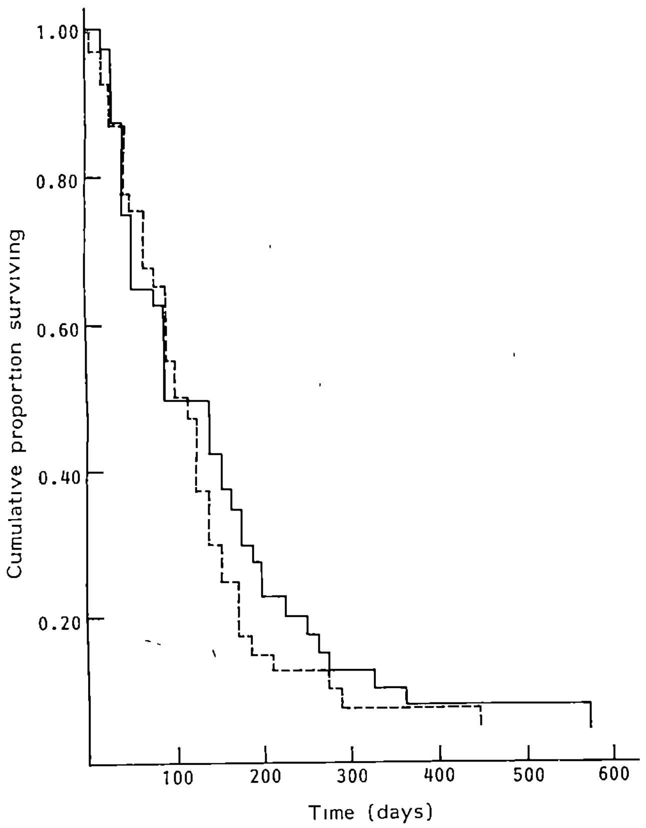

Figure 2 *Life table analysis of total survival for all randomized male patients; log rank test* P=0·4138, *power=0·334,* (----), *tamoxifen group,* (——), *placebo group*

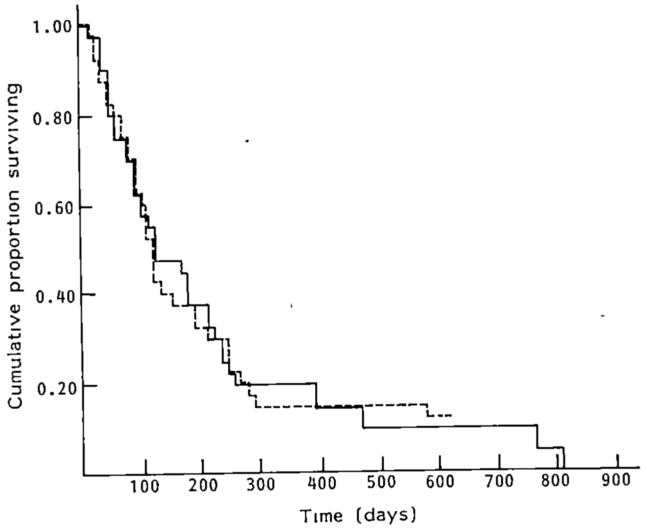

Figure 3 *Life table analysis of total survival for all randomized female patients, log rank test* P=0·8549, *power=0·261;* (----), *tamoxifen group,* (——), *placebo group*

Table 6 *Long-term survival in patients randomized to tamoxifen or placebo*

	Tamoxifen group			Placebo group		
Time (years)	No of men (*n*=48)	No of women (*n*=44)	Total (*n*=92)	No. of men (*n*=47)	No. of women (*n*=37)	Total (*n*=84)
1	1 (2)	7 (16)	8 (9)	3 (6)	4 (11)	7 (8)
1·5	0	7 (16)	7 (8)	3 (6)	2 (5)	5 (6)
2	0	3 (7)	3 (3)	2 (4)	2 (5)	4 (5)
2·5	0	3 (7)	3 (3)	0	0	0
3	0	2 (5)	2 (2)	0	0	0

Values in parentheses are percentages

statistically significant differences, the results, therefore, neither support not exclude the suggestion by Wong *et al.*[35] regarding an effect of tamoxifen in postmenopausal women. Probably the improved survival in this small subgroup of women is incidental and not a beneficial effect of tamoxifen. Proof of the suggestion by Wong *et al.* can be obtained only by conducting a controlled trial in postmenopausal women.

In conclusion, oral tamoxifen seems to be ineffective in the treatment of patients with unresectable pancreatic carcinoma.

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Participating Norwegian hospitals

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Changing patterns of incidence and mortality from acute pancreatitis in Scotland, 1961–1985

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Data on all discharges from hospitals in Scotland have been recorded since 1961 as the Scottish Hospital In-Patient Statistics and examination of these data has permitted analysis of the incidence and mortality trends from acute pancreatitis. The number of discharges recorded has increased 11-fold in males from 69 patients/year in 1961 to 750 patients/year in 1985, and fourfold in females from 112 patients/year to 484 patients/year respectively. This increase has occurred particularly amongst young and middle-aged males (20–59 years) and in elderly females (over 60 years), the most marked increases occurring in the health boards of the 'central belt' area of Scotland. Mortality rate did not show a corresponding change, increasing only two-fold in males from 15 patients/year to 30 patients/year and in females from 29 patients/year to 37 patients/year. As a consequence the case mortality rate has fallen from 17·8 per cent over the period 1961–65 to 5·6 per cent over the period 1981–85. An apparent increase in the incidence of acute pancreatitis may be inferred from these data, much of which is thought to be due to improved accuracy in diagnosis.

Keywords: Acute pancreatitis, incidence, mortality

Acute pancreatitis appears to be becoming more common but few studies have examined the changing incidence and mortality trends. A study from Bristol of the 18-year period 1950–1967 demonstrated an increasing incidence during the first 6 years of the study and a second peak of incidence between 1961 and 1964[1]. The earlier increase was attributed to wider application of amylase testing and the latter increase to locally heightened interest. Both increases were considered to be due to improvements in diagnosis rather than to an absolute change in incidence[1] and was thus similar to the experience in Rochester, Minnesota reported in 1972[2]

The Bristol study was recently updated; the incidence of acute pancreatitis increased by 26 per cent over the previous two decades but the overall case mortality rate had remained unchanged at around 20 per cent throughout this 30-year period[1,3]. This suggested that improvements in therapy introduced during this period may have failed to influence mortality

The aims of this study were to document the incidence and mortality from acute pancreatitis in Scotland and to examine any emerging trends.

Patients and methods

Data on the discharge diagnosis of all patients admitted to hospital in Scotland have been recorded on a standard form, the SMR 1, since 1961 and collated as the Scottish Hospital In-Patient Statistics[4] Details of the number of patients with a primary discharge diagnosis of acute pancreatitis (ICD Code 577 0) have been obtained for each year between 1961 and 1985 (the last year for which complete figures were available) from the Scottish Health Service Common Services Agency (Information and Statistics Division), Edinburgh. The computer printout provided details of the total number of patients and the number in whom a fatal outcome was recorded each year, with a breakdown of their age, sex and health board area No information was available from this source on the diagnostic criteria used, nor on the underlying aetiology or whether the attack was recurrent Details of the estimated population of Scotland for each year of the study were obtained from published data[5]

Results

Overall population trends

Throughout the 25-year period studied the estimated mean(s.d.) population of Scotland remained fairly stable at 5 201 900(28 600). The population peaked at 5 240 800 during the 5-year period 1971–1975 and has since fallen by 2 per cent

Incidence and mortality trends

Throughout the 1960s the number of discharges from acute pancreatitis recorded each year rose steadily, but the largest increase occurred during the 6-year period after 1971 (*Figure 1*). This trend has since tended to plateau in females while continuing to increase in males, albeit at a slower rate. Discharges in males have increased almost 11-fold since 1961 from 69 patients/year to 750 patients/year in 1985, increasing over fourfold in females during the same period from 112 patients/year to 484 patients/year in 1985 (*Figure 1*). This trend has occurred amongst adult males of all ages, particularly young

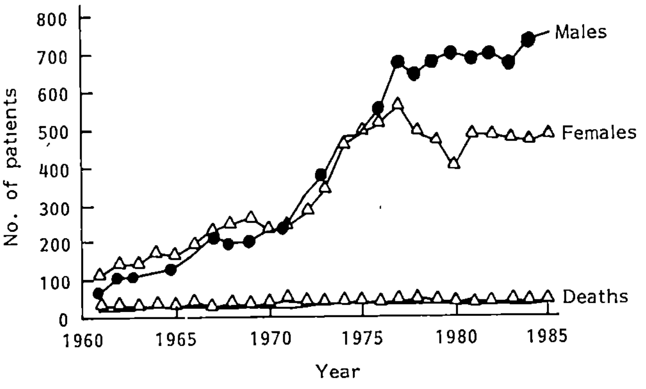

Figure 1 *Annual incidence and mortality from acute pancreatitis in Scotland by recorded discharge diagnoses, 1961–1985*

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men between 20 and 39 years of age (*Figure 2*). In females the major increase was observed amongst those over 60 years of age (*Figure 3*).

The number of deaths recorded has not shown a corresponding change, doubling in males from 15 patients/year in 1961 to 30 patients/year in 1985, and increasing only slightly in females from 29 patients/year to 37 patients/year in 1985 (*Figure 1*). Taken in conjunction with the marked increase in the number of discharges recorded, this has resulted in a dramatic fall in the overall case mortality rate amongst both sexes (*Table 1*). The mortality occurred predominantly within the >60 years age group which, in females, accounted for 56 per cent of the discharges and 81 per cent of the deaths compared with only 32 per cent of the attacks and 61 per cent of the deaths in males.

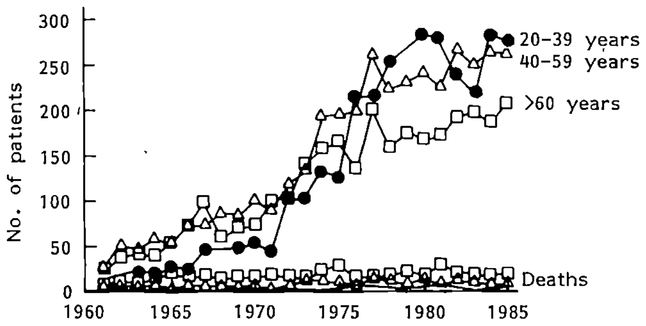

Figure 2 *Annual incidence and mortality from acute pancreatitis in men analysed by age (excluding patients <20 years old)*

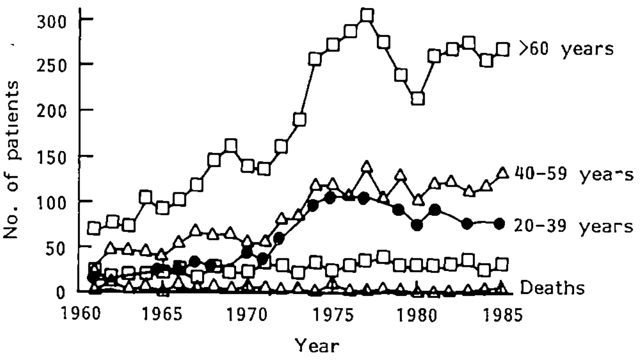

Figure 3 *Annual incidence and mortality from acute pancreatitis in women analysed by age (excluding patients <20 years old)*

Regional variations

Wide regional variations were apparent in the number of discharges recorded in each health board area during successive 5-year periods, the greatest increase (813 per cent) occurring within Argyll and Clyde (*Table 2*). In contrast, Dumfries and Galloway recorded only a 243 per cent increase during the 25 years of the study against a national average of 471 per cent (*Table 2*). These differences are shown graphically in *Figure 4*. The largest increases were recorded in the health boards of the 'central belt' area of Scotland, the more remote areas showing the smallest increases. The overall case mortality rates recorded in each region (*Table 3*) ranged widely during the period 1961–1965, although in the most recent 5-year period they are now more comparable.

Discussion

An increase in the incidence of acute pancreatitis may be inferred from the increasing number of discharges recorded in the Scottish Hospitals In-Patient Statistics, but this may be an apparent rather than a true increase in incidence. The greatest increase occurred after 1971, coinciding with the introduction of the Phadebas® test (Pharmacia Diagnostics, Uppsala, Sweden), a simple, reproducible assay for amylase In the early years of the study acute pancreatitis was often diagnosed with confidence only at laparotomy or post mortem, biochemical tests for amylase being characteristically complicated, time-consuming and infrequently utilized Nowadays the serum

Table 1 *Case mortality rate (deaths as a proportion of recorded attacks) from acute pancreatitis in Scotland, 1961–1985*

	Males		Females		Total	
Year	No.	Deaths	No.	Deaths	No.	Deaths
1961–65	543	94(17·3)	731	133(18·2)	1274	227(17·8)
1966–70	1009	109(10·8)	1156	155(13·4)	2165	264(12·2)
1971–75	1924	144(7·5)	1811	170(9·4)	3735	314(8·4)
1976–80	3265	155(4·7)	2431	189(7·8)	5696	344(6·0)
1981–85	3550	161(4·5)	2391	170(7·1)	5941	331(5·6)

Values in parentheses are percentages

Table 2 *Incidence and percentage increase of acute pancreatitis discharges recorded in the 12 major health boards, 1961–1985*

Health Board	1961–65	1966–70	1971–75	1975–80	1981–85
Argyll and Clyde	70	108(154)	236(337)	433(618)	569(813)
Forth Valley	37	113(305)	141(381)	230(622)	280(757)
Lanarkshire	87	122(140)	303(348)	443(509)	568(653)
Fife	73	142(194)	243(333)	436(597)	456(625)
Greater Glasgow	254	442(174)	876(345)	1429(563)	1480(583)
Tayside	117	223(191)	376(321)	482(412)	505(432)
Lothian	211	392(186)	528(250)	807(382)	806(382)
Ayrshire and Arran	68	93(137)	200(294)	274(403)	259(381)
Borders	40	34(85)	68(170)	62(155)	122(305)
Highland	56	71(127)	111(198)	157(280)	168(300)
Grampian	181	316(175)	453(250)	524(290)	508(281)
Dumfries and Galloway	42	54(129)	88(209)	117(278)	102(243)
Totals	1236	2110(171)	3623(293)	5394(436)	5823(471)

Values in parentheses indicate percentage change in incidence compared with 1961–65 (100 per cent)

Table 3 *Changing case mortality rates from acute pancreatitis recorded in the 12 major health boards, 1961–1985*

Health board	1961–65	1966–70	1971–75	1976–80	1981–85
Borders	10(25)	8(23·5)	3(4)	7(11)	4(3)
Argyll and Clyde	17(24)	21(19·5)	20(8·5)	23(5)	23(4)
Fife	21(29)	17(12)	19(8)	21(5)	20(4)
Dumfries and Galloway	8(19)	6(11)	10(11)	8(7)	5(5)
Tayside	19(16)	25(11)	29(8)	29(6)	27(5)
Grampian	24(13)	41(13)	30(6·5)	36(7)	24(5)
Lothian	25(12)	32(8)	38(7)	42(5)	38(5)
Lanarkshire	22(25)	20(16)	26(9)	28(6)	34(6)
Greater Glasgow	36(14)	54(12)	76(9)	85(6)	90(6)
Forth Valley	5(13·5)	4(3·5)	14(10)	13(6)	17(6)
Highland	11(20)	11(15·5)	14(13)	17(11)	12(7)
Ayrshire and Arran	21(31)	20(21·5)	26(13)	19(7)	29(11)
Total	219(18)	259(12)	305(8·5)	328(6)	323(5·5)

Values in parentheses are percentages of incidence figures shown in *Table 2*

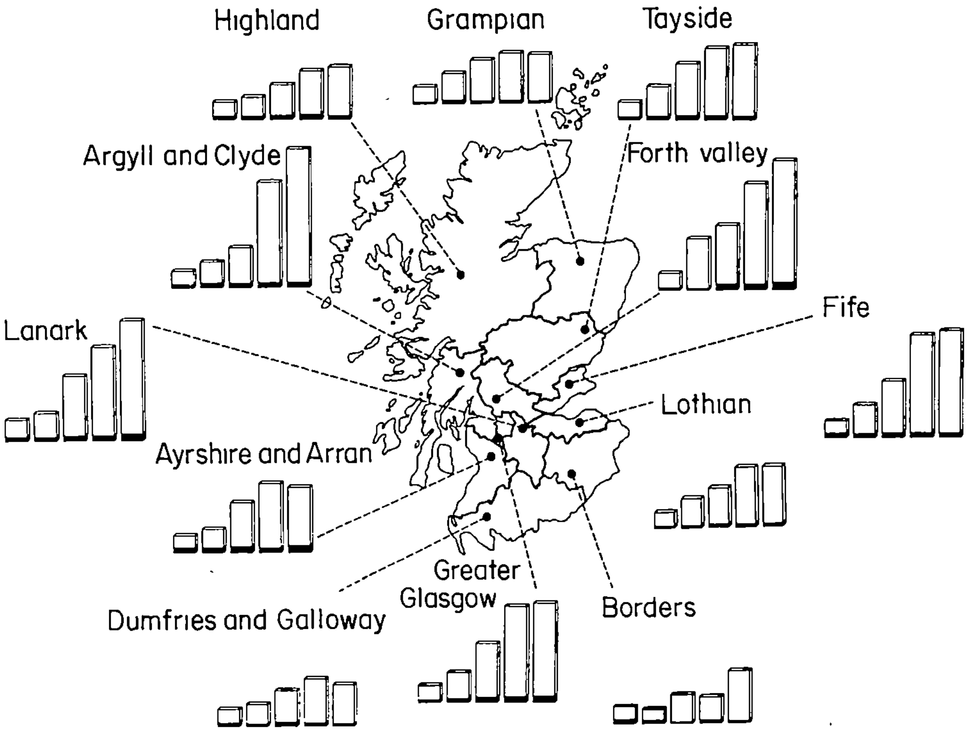

Figure 4 *Variation in incidence, ☐, and mortality, ■, from acute pancreatitis in the 12 major health board regions of Scotland expressed as the percentage increase during successive 5-year periods compared with the period 1961–1965 (Analysis excludes Orkney, Shetland and the Western Isles Health Boards where too few cases were recorded to permit useful analysis)*

amylase activity is measured on almost all patients presenting to hospital with upper abdominal pain of acute onset and it is likely that this has led to the diagnosis being established in a greater proportion of those with acute pancreatitis. Increased awareness of the condition in the past 20–30 years may also be a factor in its increasing diagnosis, perhaps dating from several important articles published at that time[6,7].

The number of discharges recorded continued to increase in males throughout the late 1970s and early 1980s, while appearing to have levelled out in females Such a change favours a true increase in the incidence amongst males which may be alcohol related[8] Recurrent attacks, requiring repeated admissions, are also more common in association with alcoholic pancreatitis and may be an additional factor contributing to the continuing increase in discharges.

The regional variations are more difficult to explain Predominantly rural areas with less easily accessible in-patient hospital care may have a greater proportion of those with mild attacks treated at home (where the diagnosis may not be made and will not be recorded) than might be the case in urban areas. Differences in life-style, with respect to the frequency, extent and nature of alcohol abuse amongst the young, often socially deprived populations within the urban areas of the central belt of Scotland must be considered and may explain some of the variation

The overall case mortality rate has fallen dramatically during the period of this study in contrast to the experience reported from Bristol[1,3]. While improved treatment of acute pancreatitis may have contributed to the falling case mortality rate, a more plausible explanation for its decline may be that the nature of the disease recorded has itself changed. An increase in the diagnostic rate, as suggested above, is likely to have resulted

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in the diagnosis being established in greater numbers of patients with mild disease. Such patients would be less likely to die and this may explain much of the fall in the case mortality rate.

The accuracy of the Scottish Hospitals In-Patient Statistics is dependent upon the quality and completeness of the data input supplied by doctors and clerical staff in the many hospitals within the 15 health boards. Computerization might be expected to improve data collection but deficiencies may remain within this system as has been highlighted by one recent survey[9]. The incidence of acute pancreatitis in the Grampian region of Scotland was investigated for the years 1983–1985 by examining the record of amylase examinations carried out in the single regional laboratory performing these assays. Only 53 per cent of the total number of cases of acute pancreatitis identified in the study has been recorded in the hospital's computer-linked diagnostic index[9]. If representative of other health boards in Scotland, this may have profound implications for the accuracy of disease reporting nationally and the number of cases reported here may be underestimating the true incidence within the hospital population by up to 100 per cent.

Subject to these drawbacks the national statistics provide a broad overview of the disease and its changing incidence. We have speculated that much of the increase in the numbers recorded may be an apparent rather than a true increase in the incidence of the disease, reflecting improved accuracy in its diagnosis. The true incidence may also be increasing, particularly amongst young and middle-aged adult males, and would be supported by the small increase in the numbers of deaths.

Acknowledgements

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Gallbladder cholesterolosis: an aetiological factor in acute pancreatitis of uncertain origin

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To investigate the possible relationship between gallbladder cholesterolosis and acute pancreatitis, we studied 3797 cholecystectomy specimens and found 55 cases of gallbladder cholesterolosis unassociated with biliary lithiasis. From the reviewed case notes, 27 of these patients presented with recurrent attacks of acute pancreatitis which disappeared after cholecystectomy (follow-up 65·1 months). A microscopic study revealed frank cholesterolosis in all cases with a pseudopolyp transformation of the mucosa, some polyps reaching a diameter of 2 mm. We postulate that the mechanism could be temporary impaction of cholesterolosis polyps at the sphincter of Oddi and suggest that patients with recurrent attacks of acute pancreatitis and negative aetiological investigation must be considered as at high risk of having gallbladder cholesterolosis and that they could benefit from cholecystectomy.

Keywords: Acute pancreatitis, gallbladder cholesterolosis

In our population more than 90 per cent of cases of acute pancreatitis are caused by one of two aetiological factors, namely cholelithiasis or alcohol[1]. Other less frequent aetiological factors include hyperlipidaemia, hyperparathyroidism, abdominal trauma and abdominal surgery. However, we cannot define the aetiology with certainty in all cases of acute pancreatitis and so cannot prevent recurrent attacks.

The association of acute pancreatitis with cholelithiasis is known to be due in more than 90 per cent of cases to the transpapillary migration of small calculi which can be found in the stool during the days following the crisis[2]. In view of the possibility of microlithiasis, two of our patients with negative ultrasonography and oral cholecystography were recommended 2 years ago to undergo cholecystectomy. We expected to find a gallbladder with microlithiasis; in the event there were no calculi in the gallbladders which were, however, affected by cholesterolosis. We then postulated that certain fragments of mucous membrane may have been detached, leading to the development of pancreatitis by obstruction of the passage of pancreatic secretions through the papilla. From this hypothesis we began a clinical investigation, the results of which are presented here.

Materials and methods

Between January 1979 and December 1988, 3797 histopathological reports on cholecystectomy specimens were made by us in the 'Virgen de la Arrixaca' University Hospital, Murcia, Spain. Cholesterolosis was found in 434 of these gallbladders. The diagnosis of cholesterolosis was accepted when the pathologist noted the presence of foamy histiocytes laden with esters of cholesterol in the lamina propria of the vesicular mucous membrane; such histiocytes were found mainly in the villi.

We then reviewed the case notes of all patients with cholesterolosis in order to determine whether they had suffered from acute pancreatitis, whether they had associated lithiasis, and to assess their progress after cholecystectomy.

A diagnosis of acute pancreatitis was accepted on the basis of the following criteria: (1) acute onset of the illness, (2) clinical data and abdominal radiographs compatible with diagnosis of acute pancreatitis, (3) urine amylase level above 1000 units/ml (normal level in our laboratory is <650 units/ml), and (4) absence of any other acute abdominal pathology.

Results

From the reviewed case notes, gallbladder cholesterolosis was associated with cholelithiasis in 379 cases (87·3 per cent), while in 55 cases (12·7 per cent) no gallstones were found. In the first group there were attacks of acute pancreatitis in 98 cases (25·8 per cent) which could be attributed to the accompanying cholelithiasis. However, in the patients with cholesterolosis but without cholelithiasis there were attacks of acute pancreatitis in 27 cases (49 per cent). It is essential to note that all aetiological investigations in these patients to determine the association of pancreatitis with alcohol, abdominal trauma, abdominal surgery, hyperparathyroidism, hyperlipidaemia or pancreas divisum had negative results.

Twenty of these patients were women and seven were men, with a mean age of 52·8 years (range 23–68 years). The time between the last attack of acute pancreatitis and cholecystectomy averaged 3·2 months (range 2–11 months). There were fundamentally two indications which had led to cholecystectomy in these 27 patients: (1) attacks of acute pancreatitis with symptoms compatible with biliary lithiasis and failure to visualize the gallbladder on intravenous cholecystography (ten patients); and (2) attacks of acute pancreatitis with symptoms compatible with biliary lithiasis and ultrasonography findings suggestive of microlithiasis (17 patients).

We studied the gallbladders of these 27 patients microscopically and in all cases detected the presence of a frank cholesterolosis with a massive pseudopolyp transformation of the gallbladder mucous membrane (*Figures 1* and *2*). Macroscopically, we observed in all patients the characteristic appearance of a strawberry gallbladder, and in some the existence of polyp formation of up to 2 mm in diameter; these were connected to the gallbladder mucosa by a narrow pedicle (*Figure 3*) which was easily breakable by moving the head of the polyp.

All the patients were found to be asymptomatic on follow-up, as none of them had recorded recurrent attacks of acute pancreatitis. Follow-up averaged 65·1 months (range 12–126 months).

Discussion

The relationship between cholesterolosis and pancreatitis has not been studied sufficiently. In 1976, Andersson and Bergdahl[3] described a patient with recurrent attacks of acute pancreatitis in whom cholecystography showed no abnormality. The patient finally underwent cholecystectomy. The mucous membrane of the gallbladder contained numerous cholesterolosis polyps. After the operation, the patient remained free from symptoms.

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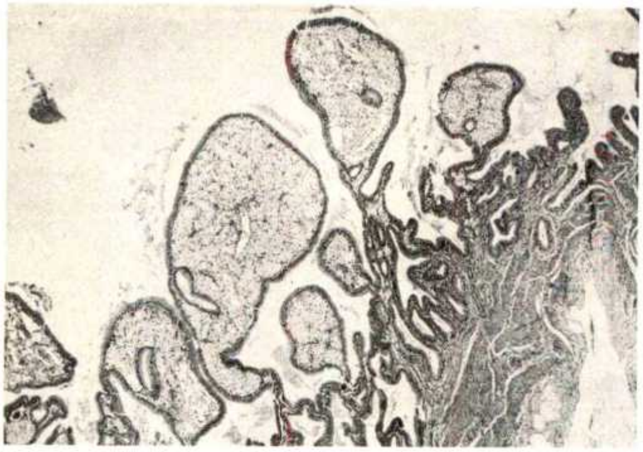

Figure 1 *Microscopic view of gallbladder affected by cholesterolosis, in which a tendency towards pseudopolyp transformation of the mucous membrane is observed (haematoxylin and eosin, original magnification × 100)*

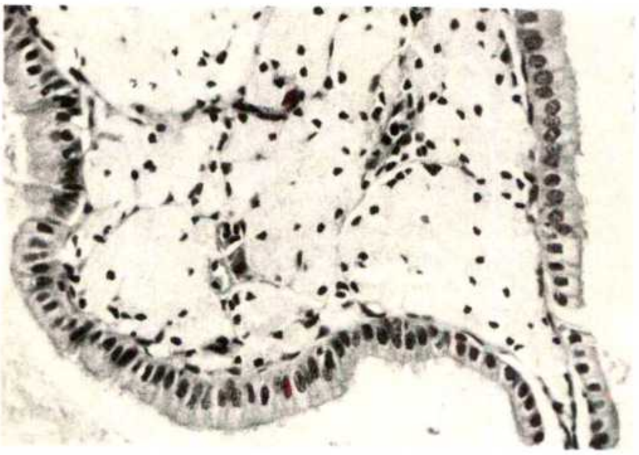

Figure 2 *View of pseudopolyp which appears to be composed of a cluster of foamy cells delimited by the lamina propria of the villi (× 400) (haematoxylin and eosin, original magnification × 400)*

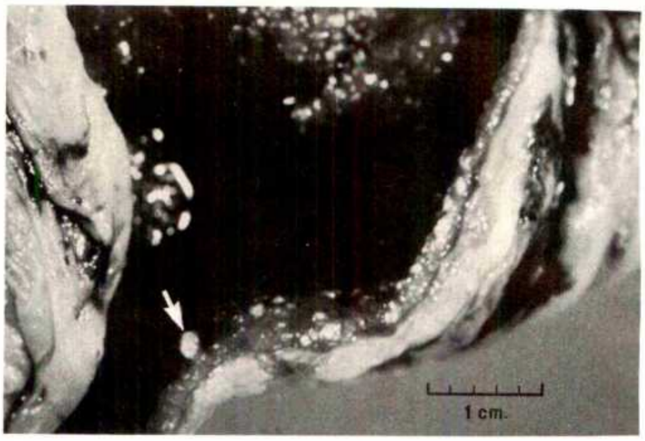

Figure 3 *Macroscopic view of the gallbladder wall presenting cholesterolosis with formation of pseudopolyps, one of which (arrowed) reaches a diameter of 2 mm*

Thus, Andersson and Bergdahl[4] suggested that jaundice could be produced by cholesterolosis.

The question that remains is how acute pancreatitis can be produced by cholesterolosis. We postulate that the mechanism could be temporary impaction of cholesterolosis polyps at the sphincter of Oddi. This obstruction would increase the pressure in the pancreatic ducts, triggering the physiopathological process that leads to acute pancreatitis.

This hypothesis is based on the following observations. First is the tendency of cholesterolosis to form polyps. This is a well known controversy for pathological specialists. Moreover, these polyps are not usually associated with fibrosis, so that they can be easily detached. Second, all patients in our series suffering from acute pancreatitis without lithiasis showed cholesterolosis polyps in the gallbladder. Investigation of these gallbladders has led us to postulate a possible sequence of formation, pediculation and detachment of these polyps. Third, jaundice has also been recognized as a complication of cholesterolosis[4] and has been attributed to obstruction of the bile duct by polyps. Fourth, it is important to note that none of our patients has suffered further attacks of acute pancreatitis since operation.

For these four reasons, we suggest that patients with recurrent attacks of acute pancreatitis and negative aetiological exhaustive investigation must be considered as at high risk of having gallbladder cholesterolosis. However, certain preoperative diagnosis is difficult and the radiologist should be asked to look for objective signs of cholesterolosis, using cholecystography or ultrasonography. Under these circumstances, we consider that the patient should be told of the possibility of a further attack of acute pancreatitis and informed that cholecystectomy may prevent this crisis.

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MAXON (polyglyconate) sutures are intended for use where an absorbable suture or ligature is indicated.

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Contra-indications, precautions, warnings etc.
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Non-slip lock knots should be used at both ends of a continuous closure. Likewise following continuous closure with a looped suture a non-slip locking knot should be employed for maximum security.

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Further information Nil.

Product licence numbers
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Date of preparation or last review May 1990.

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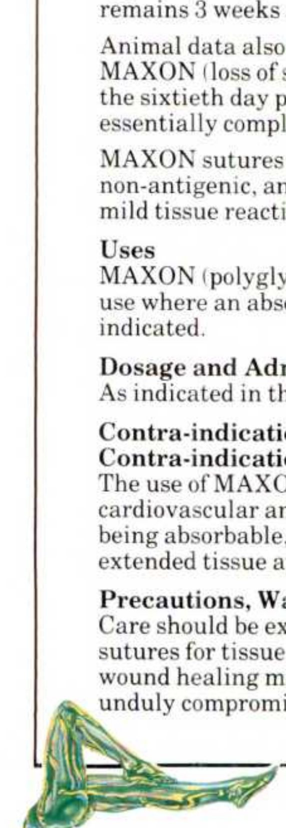

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Gallstone ileus

Thirty-seven patients (33 women and four men, median age 78 years) were operated on for gallstone ileus over a 12-year period with a median follow-up of 6·2 years. Twenty-three patients (62 per cent) had serious concomitant diseases. Plain abdominal radiographs performed at admission were diagnostic in only 17 patients (46 per cent) and other procedures such as ultrasonography, gastrointestinal contrast studies and computed tomographic scan were required in ten patients (27 per cent). The diagnosis was made before operation in 27 patients (73 per cent) but in only 17 (46 per cent) at admission. Obstructing stones were located in the terminal ileum in 27 patients (73 per cent), in the proximal ileum or jejunum in five (14 per cent), in the duodenum in two (5 per cent), and in the colon in three (8 per cent). In six instances (16 per cent), more than one stone was involved. Cholecystduodenal fistula was the most frequent fistula type (n = 25*, 68 per cent), followed by cholecystcolonic* (n = 2*, 5 per cent) and cholecystduodenocolonic* (n = 2*, 5 per cent) types. The site of the fistula was not established in the other eight instances. A one-stage procedure consisting of the removal of the impacted stone, fistula repair and cholecystectomy was performed in eight patients, two of whom died. A second group of six patients underwent a two-stage procedure consisting of enterolithotomy followed by elective biliary surgery, with no mortality. Removal of impacted stones was the only surgical treatment in the remaining 23 patients, with five deaths. Operative mortality and morbidity rates associated with the initial procedure did not differ significantly among the three therapeutic groups, which were comparable in terms of patient age, associated concomitant diseases and APACHE II score. However, later biliary complications were prominent in patients treated only by enterolithotomy. These results support the view that a one-stage procedure is, when feasible, a valid option and may be the procedure of choice. When local or surgical conditions argue against a one-stage procedure, biliary surgery at a second stage should be considered, if residual stones are present. In poor risk patients, non-operative methods should be considered.*

Keywords: Gallstone ileus, radiology, treatment, biliary surgery, recurrence

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Longevity in Western countries has probably increased the prevalence of gallstone ileus. In the past, few authors have reported more than one case per year[1–5]; however, in recent years, we have encountered more than three cases per year at the University Hospital of Geneva.

Gallstone ileus is a troublesome surgical disorder. It is often misdiagnosed and carries a significant rate of complications and a mortality rate ranging between 12 and 27 per cent in most series reported in the past 30 years[1,3–12]; its danger reflects the advanced age of patients and the high incidence of severe concomitant diseases. Some authors recommend surgical removal of the obstructing stone from the gut and avoid biliary surgery so as to reduce operative time and postoperative mortality rate[2,8,13–16]. On the other hand, some authors emphasize that fistula repair and cholecystectomy should also be undertaken whenever possible, either during the initial procedure[4,17–19] or at a second staged operation[9].

The purpose of the present study is to review the clinical syndrome, the risk factors, the radiological and operative findings and the postoperative course of patients with gallstone ileus in a region of high incidence. The various surgical procedures will be evaluated in terms of morbidity, mortality and incidence of recurrent biliary symptoms. All patients alive at the time of the survey were re-examined at a median interval of 6·2 years (range 2–15 years) from their initial presentation.

Patients, methods and results

From January 1976 to December 1987 thirty-seven patients were treated for gallstone ileus at our hospital, representing 1·7 per cent of 2197 patients admitted with mechanical bowel obstruction during that period. The incidence rose from 0·7 per cent in the age group under 70 years to 4·8 per cent in older patients ($P < 0{\cdot}001$, χ^2). Gallstone ileus also represents 0·6 per cent of 6643 patients who underwent biliary surgery during the same period.

The group included 33 women and four men. The median age was 78 years (range 55–92 years); 27 patients (73 per cent) were over 70 years of age. The severity of the disease on admission was evaluated by the APACHE II grading system[20] and scores ranged from 5 to 34, median 16·5. Twenty-three patients (62 per cent) had serious concomitant disease, involving one system in 15 cases and two systems or more in the other eight patients. Cardiovascular disorders were noted in 20 patients, pulmonary disorders in six, renal disease in four and digestive disease in one. In addition, eight patients (22 per cent) had diabetes mellitus, an incidence not significantly different from that found in a random group of 50 elderly patients (aged >70 years) with acute abdominal emergencies ($P = 0{\cdot}7$, χ^2).

Clinical syndrome, laboratory tests and imaging procedures

Sixteen patients (43 per cent) had a past history of biliary disease, but only three (8 per cent) had documented cholecystitis during the preceding year. None had undergone previous biliary surgery. Symptoms lasted for a median of 5 days before admission (range from 6 h to 22 days).

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Abdominal pain was constantly present and accompanied by vomiting in all but one patient. Pain was clearly described as cramping or 'waning and waxing' in more than two-thirds of the cases. The clinical presentation was consistent with bowel obstruction in 26 patients (70 per cent), with cholecystitis in seven (19 per cent) and with both in four (11 per cent). Laboratory tests were non-specific with a median leucocyte count of $12{\cdot}6 \times 10^9$ cells/l (range $6\text{–}21 \times 10^9$ cells/l). Liver function tests were abnormal in 15 patients (41 per cent) and the plasma amylase level was twice the normal value in one. Electrolyte imbalance was noted in 22 patients (59 per cent).

All patients had plain abdominal films taken on admission. Seventeen (46 per cent) showed at least two of the three classical signs of gallstone ileus while four patients (11 per cent) had none (*Figures 1* and *2*). Nine of our patients (24 per cent) presented with two adjacent small air-fluid levels in the right upper quadrant (*Figure 2*), a finding not associated with the presence of air in the hepatic and common bile ducts in four instances. Decisive further information regarding the diagnosis was obtained by ultrasonography in six patients (*Figure 3*), gastrointestinal contrast studies in three patients, and computed tomographic scan in one (*Figure 4*). Finally, in two patients with signs of proximal obstruction gastroduodenoscopy demonstrated duodenal obstruction, first interpreted as due to a phytobezoar. One was operated on with this diagnosis and the other had the correct preoperative diagnosis made by contrast radiology (*Figure 5*). Nine patients had preoperative arteriography which was carried out after a spurious diagnosis of mesenteric ischaemia had been made.

Gallstone ileus was diagnosed before operation in 27 patients (73 per cent) but in only 17 (46 per cent) upon admission. Duration between admission and operation ranged from 5 h to 14 days (median 2·5 days), a delay which often resulted from the intermittent nature of the symptoms and signs, the need to correct electrolyte disturbances and need for resuscitation of the patients.

Operative findings

Bowel obstruction was located in the terminal ileum in 27 patients (73 per cent) (including three cases where the obstruction occurred at the ileocaecal valve), in the proximal ileum or jejunum in five patients (14 per cent), in the duodenum in two (5 per cent) and in the sigmoid colon in three (8 per cent). In the three latter sites, the stone was impacted at a narrowing of the lumen corresponding to a postdiverticulitis stenosis. In 31 cases (84 per cent) a single stone was found in the gut, whereas in six (16 per cent) lithiasis was multiple (one had four stones). The size of obstructing stones is known in 32 patients and their smallest diameter ranged from 2 to 5 cm (median 3·5 cm).

Cholecystduodenal fistula was by far the most frequent connection between gallbladder and bowel ($n=25$, 68 per cent) followed by cholecystcolonic fistula ($n=2$, 5 per cent) and cholecystduodenocolonic fistula ($n=2$, 5 per cent). Marked inflammation in the right hypochondrium did not allow any conclusions regarding the presence of a fistula at the time of surgery in 16 patients. However, in eight of these patients, contrast radiology and ultrasonography enabled identification of the fistulae during the postoperative period. Thus, the course of the fistula remained unclear in only eight patients.

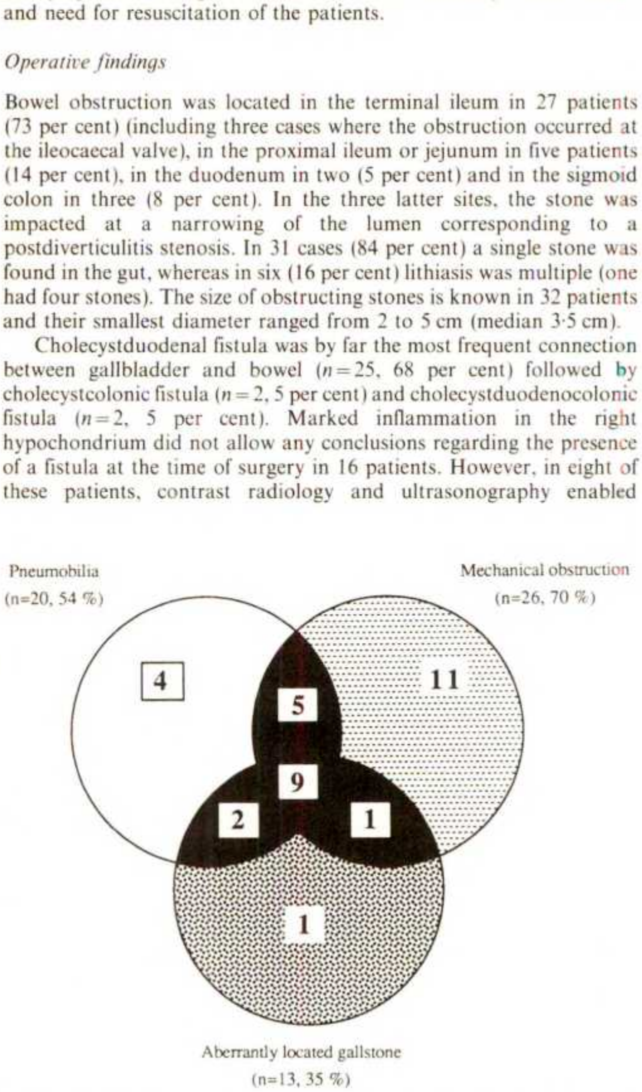

Figure 1 *Findings on plain abdominal radiography at admission of 37 patients with a first episode of gallstone ileus. Seventeen patients (46 per cent) presented two or more radiological signs (■) and four patients (11 per cent) had none*

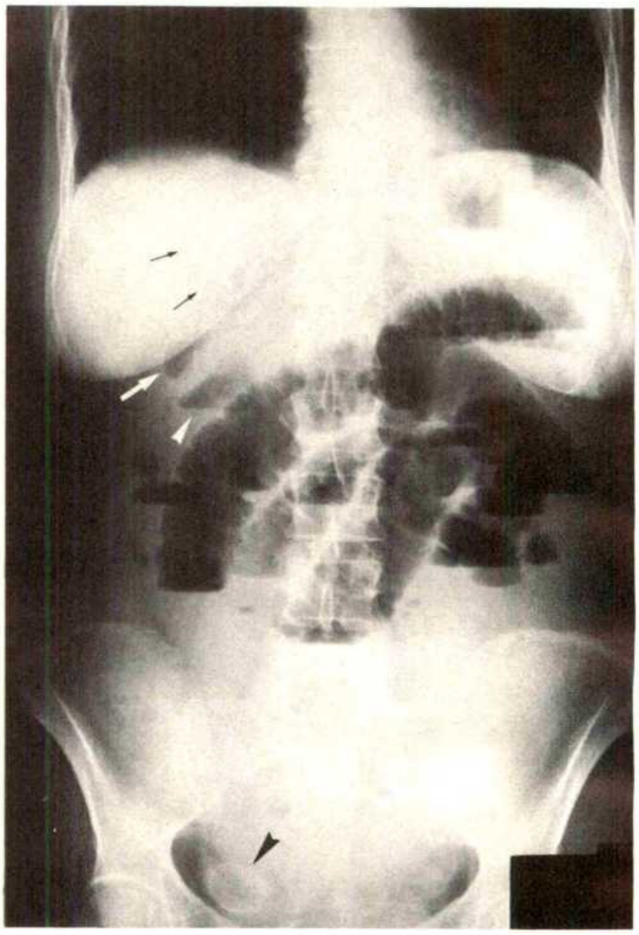

Figure 2 *A plain abdominal radiograph at admission with the typical triad of pneumobilia (black arrows), mechanical ileus, and an aberrantly located gallstone (black arrowhead). Balthazar's sign consists of air in the gallbladder (white arrow) and in the duodenal bulb (white arrowhead)*

Surgical procedure

All patients underwent surgical treatment (*Table 1*). Twenty-three had surgery focused exclusively on the obstructing stone. The most common procedure was an enterolithotomy alone, but other procedures were performed such as small bowel resection in two patients for intestinal perforation and a Hartmann's operation in one for sigmoid stenosis with active diverticulitis. Finally, in one patient, a single stone in the terminal ileum was evacuated *per anum* by milking it down the gut without enterotomy.

Six patients were managed by a two-stage procedure consisting initially of enterolithotomy; one patient had gastrotomy for the extraction of a stone impacted at the site of duodenal stenosis secondary to chronic pancreatitis, two others had resection with end-to-end anastomosis because of sigmoid stenosis. Fistula repair and cholecystectomy were then carried out within 4 weeks of the initial operation because of residual cholelithiasis.

Finally, eight patients underwent a one-stage procedure in which enterolithotomy and biliary repair were performed at one operation. The choice of this aggressive treatment was always based on the presence of cholelithiasis as demonstrated before operation by ultrasonography in all but one case; in this latter instance, stones in the gallbladder were palpated at operation. Six of these eight patients had intraoperative cholangiography which demonstrated multiple choledocholithiasis in one case, successfully treated by choledochotomy.

There were no statistical differences among the three therapeutic groups in age, in incidence of serious concomitant disease or in the admission APACHE II score (Mann–Whitney *U* test).

Clinical course (Table 1)

There were no significant differences in the hospital mortality rate between groups of patients treated exclusively by surgery to deal with

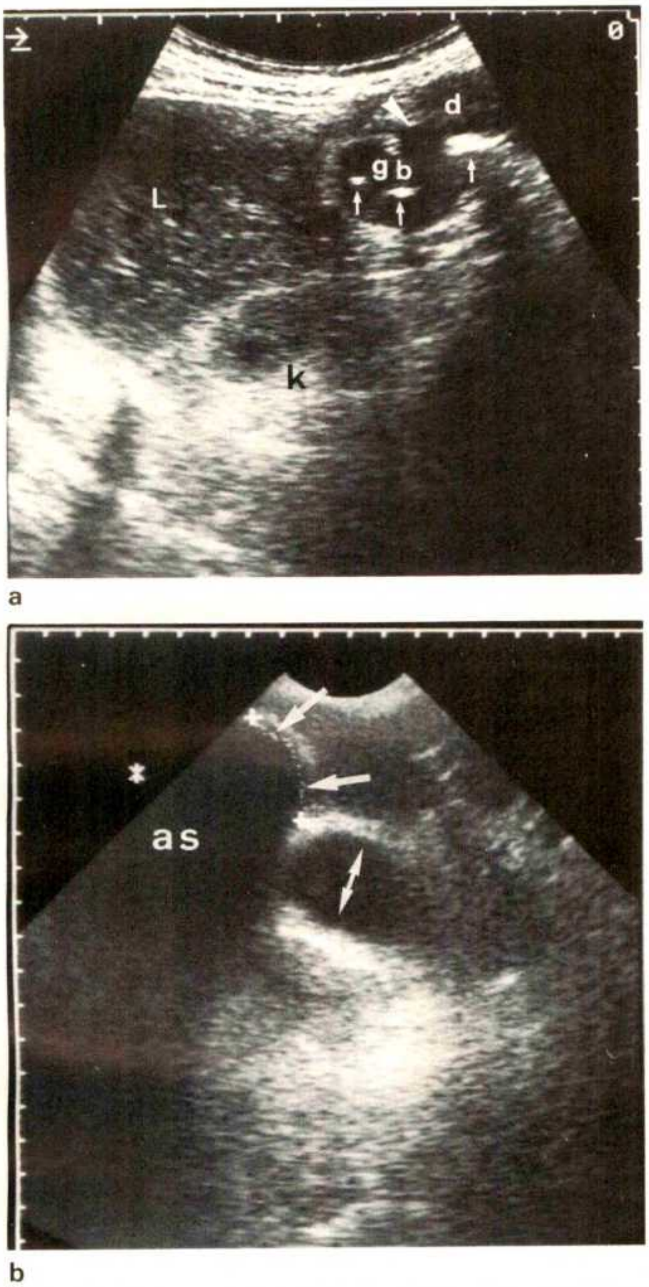

Figure 3 *Ultrasonography at admission demonstrating* **a** *the fistula (arrowhead) between the gallbladder (gb) and the duodenal bulb (d), the presence of air (small arrows) in the gallbladder and the duodenal bulb, and* **b** *the impacted gallstone in the ileum (large arrows) with an important acoustic shadow (as) and dilatation of a proximal ileal segment (double-headed arrow). L, liver; K, kidney*

the intestinal stone (five deaths in 23 patients, 22 per cent), by a two-stage procedure (no deaths in six patients) or by a one-stage procedure (two deaths in eight patients, 25 per cent) (χ^2 test with Yates' correction). The overall mortality rate was 19 per cent (seven out of 37 patients). Of the seven deceased patients, three died from cardiac failure, two from pulmonary emboli and two from multiple organ failure with sepsis. The latter two patients underwent relaparotomy which revealed leakage from the intestinal suture line in one. The cause of sepsis could not be identified in the second patient.

Morbidity was generally high with a median hospital stay of 27 days (range 12–76 days) and was not related to the type of surgical treatment. Postoperative complications, other than relapsing gallstone ileus, occurred in 19 of 30 survivors (63 per cent) and, in spite of systemic antibiotic prophylaxis, were due primarily to wound infections ($n=8$, 27 per cent). Wound dehiscence occurred in one patient, deep venous thrombosis in three, pneumonia in two, lung emboli in one, and other cardiopulmonary disorders in four patients.

Biliary complications were prominent in the 23 patients who underwent surgery only to deal with the obstructing stone. Four patients developed recurrent gallstone ileus, two during hospitalization (at the 18th and 25th day), and two others after hospital discharge (after 1 and 7 months). At the initial operation the entire gut had been carefully palpated in the four patients in order to exclude residual stones. Thus, it appears that recurrence resulted from migration of new stones through the existing fistulae. These four patients were reoperated on using a one-stage procedure; one died 6 days after surgery from multiple organ failure and the three others had no further complications.

Three other patients, who had surgery only on the obstructing stone, were reoperated on because of acute cholecystitis ($n=2$) or acute cholangitis ($n=1$) after 7 months, 9 months and 3 years, respectively. In two of these three patients cholelithiasis had been diagnosed at the time of gallstone ileus, but both had refused biliary surgery at that time.

Seven patients, treated by enterolithotomy alone, were still alive at the time of this survey. Three complained of symptoms related to biliary disease; ultrasonography and gastrointestinal contrast studies were performed on two patients and showed persistent biliary–enteric fistulae in two and cholelithiasis in one. Biliary surgery was, therefore, proposed. The third patient, who was 92 years old and in poor general condition, refused any investigations. Four of the seven patients still alive had no biliary symptoms; three of them accepted ultrasonography and gastrointestinal contrast studies which demonstrated the absence of persistent fistula and residual cholelithiasis. Finally, all deaths that

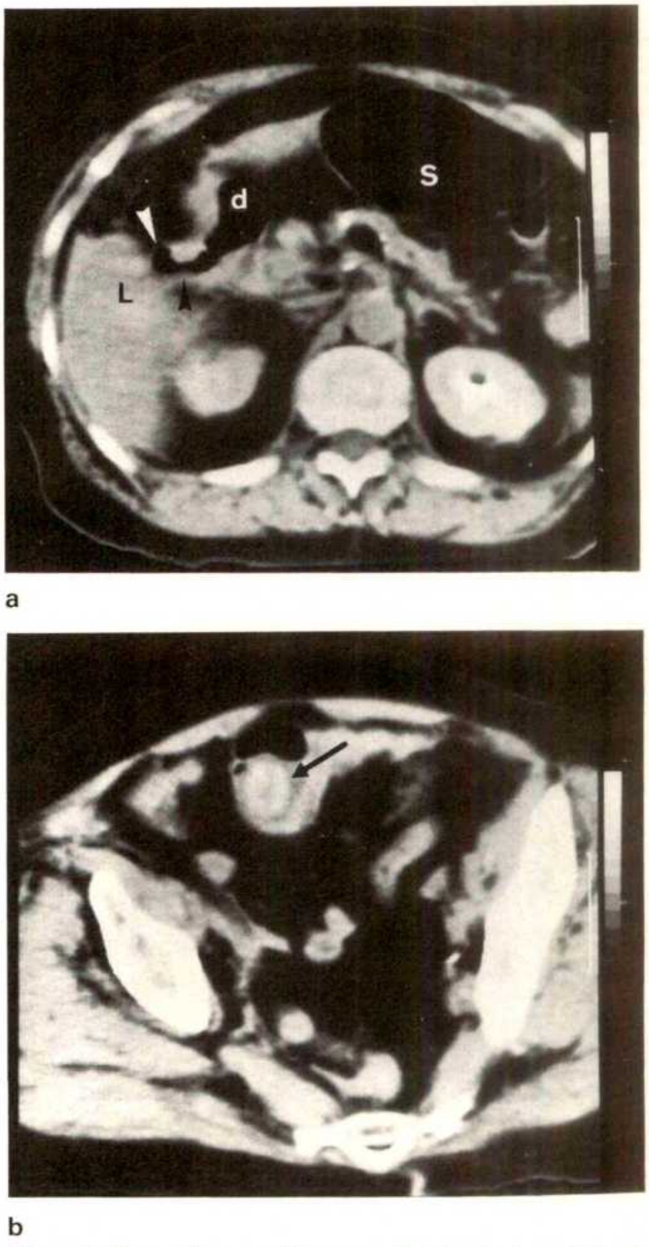

Figure 4 *Computed tomographic scan at admission showing* **a** *the fistula (black arrowhead) between the infundibulum of the gallbladder (white arrowhead) and the duodenal bulb (d) and* **b** *the obstructing stone in a dilated ileal segment (arrow). S, stomach; L, liver*

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Table 1 *Treatment and follow-up of 37 patients with gallstone ileus*

	No. of patients	Operative mortality*	Late mortality* unrelated to biliary disorders	Alive free from symptoms	Alive with symptoms related to biliary disorders	Recurrent gallstone ileus†	Acute cholecystitis	Acute cholangitis
Surgery on the impacted stone only	23	5	4	4	3	4	3	1
Two-stage procedure	6	0	3	3	0	0	0	0
One-stage procedure	8	2	1	5	0	0	0	0

* Operative mortality refers to deaths that occurred during hospitalization and late mortality refers to deaths that occurred after hospital discharge; † all four patients with recurrent gallstone ileus underwent a one-stage procedure, one died after operation and three are alive and free from symptoms

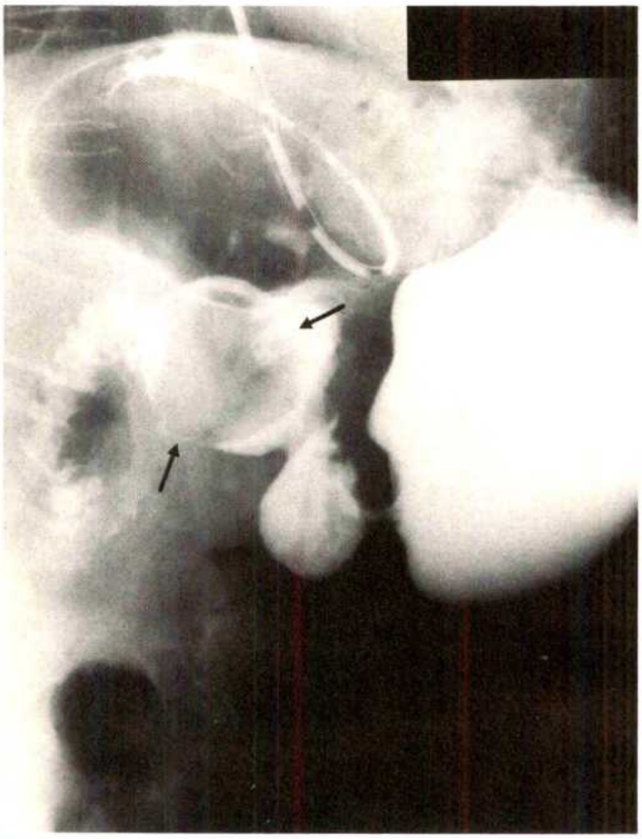

Figure 5 *Preoperative gastrointestinal contrast study showing a stone impacted in the duodenum (arrows). Massive gastric dilatation present on a previous plain abdominal radiograph has disappeared due to gastric suction*

occurred after hospital discharge were not related to biliary disease. Thus, subsequent biliary disorders occurred in ten of the 18 survivors (56 per cent) treated primarily only by surgical removal of the obstructing stone.

None of the patients treated by the one-stage or two-stage procedures developed complications related to biliary disorders.

Discussion

Gallstone ileus is a geriatric surgical emergency accounting for 1–4 per cent of mechanical intestinal obstructions[1,3,11,12,15]. In our institution the incidence was 0·7 per cent before 70 years of age and 4·8 per cent thereafter. We have treated an average of 3·2 cases of gallstone ileus per year in a hospital which serves a population of about 360 000, an incidence of about one case per 117 000 people per year. To our knowledge, this is the highest incidence reported.

The disease occurs more frequently in women than in men in a ratio usually ranging between 4:1 and 16:1[4–7,12,13,17,18]. We report an 8:1 ratio. The median age in our series of 78 years is slightly higher than the usually reported range of 65–75 years[1–8,11–14,17,18]. The youngest patient in our study was 55 years old, but patients as young as 13 years of age have been reported[9].

The clinical presentation of gallstone ileus is rarely specific and more than one-third of patients have no history of biliary symptoms[1–4,6–9,11]. In our series, less than half of the patients had symptoms consistent with biliary disorders, and previous cholecystitis was noted in only three instances. The duration of symptoms before admission is reported as varying from 4 to 8 days[1,2,4–9,11–13] and was 5 days in our series. This interval reflects the intermittent movement of gallstones until eventual impaction (tumbling obstruction). Mechanical intestinal obstruction with abdominal pain and vomiting is the most common clinical presentation as seen in 80 per cent of our patients. Proximal obstruction is characteristically accompanied by bilious vomiting and gastric dilatation, whereas faeculent vomiting and bowel distension are often prominent in ileal or sigmoid obstruction[7,11]. Jaundice is uncommon and is found in less than 15 per cent of cases[2,7,11]. Laboratory tests may reveal slight leucocytosis, electrolyte imbalance and signs of dehydration[1,2,6,7,11] and are, therefore, of little diagnostic value. Liver function tests are abnormal in about one-third of the patients[9,11]; 41 per cent in the present study. Some laboratory results can be misleading and one of our patients with hyperamylasaemia was initially treated for acute pancreatitis.

Concomitant geriatric diseases are present in as many as 80–90 per cent of cases[1,2,6,7,12]. Two-thirds of our patients presented with a debilitating disease unrelated to the biliary tract; cardiovascular disorders were most frequent. Diabetes mellitus has been found in up to 40 per cent of the patients with gallstone ileus[7]. Like others[9,11], we did not confirm this association in the 37 patients we studied.

Classical findings on plain abdominal radiography[21] include: (1) pneumobilia, (2) intestinal obstruction, (3) aberrantly located gallstone, and (4) change of location of a previously observed stone. The presence of two of the three first signs has been considered pathognomonic of gallstone ileus[1,6,7] and is encountered in 40–50 per cent of the cases[4,9,11]. The most frequent finding on our admission radiographs was mechanical obstruction (70 per cent) followed by pneumobilia (54 per cent) and, finally, by the presence of an abnormally located gallstone (35 per cent). Pneumobilia has been found in as many as 90 per cent of cases[7,21], but was present in 60 per cent of patients in most studies[2,4,9,11,22]. Pneumobilia implies either a patent cystic duct or a fistula involving the common bile duct. In the majority of patients, cystic duct obstruction is the pathophysiological event which causes cholecystitis and eventually leads to biliary–enteric fistula[22,23]. This explains why the air is frequently absent from the biliary tree. Some authors regard pneumobilia as a favourable finding, implying a high probability of spontaneous fistula healing as the gallbladder can drain normally through the common bile duct[18]. It must be emphasized that air in the biliary tree is not specific to gallstone ileus since half of the cases of pneumobilia are related to previous biliary surgery or an incompetent sphincter of Oddi[16,23,24]. Ten years ago, an interesting radiological sign, associated with gallstone ileus, was described and consists of two adjacent small air-fluid levels in the right upper quadrant, the medial collection being in the duodenal bulb and the lateral in the gallbladder[24] (*Figure 2*). This sign was present on admission in nine of our patients (24 per cent) and, interestingly, was not associated with air in the hepatic or common bile duct in four of them. Visualization of stones outside the biliary region is often difficult because of the superimposition of gaseous or bony contours and the radiolucency of most stones[4,6,7].

Ultrasonography is extremely useful in detecting a fistula, impacted stones and the presence of residual cholelithiasis and/or choledocholithiasis[25]. Contrast radiology is also valuable as a means of identifying the course of the fistula and the level of bowel obstruction[2,3,7,10,22]. Gastroduodenoscopy enables direct visualization of stones impacted in the duodenum[26] and it has been suggested that such stones can be removed endoscopically[27]. Recently, a case of gastric outlet syndrome caused by a giant gallstone was successfully treated by shock-wave lithotripsy[28].

In most series, the diagnosis is made before operation in less than half of the patients[1–4,7–9,11], although this diagnosis rate may increase to 74 per cent at the time of operation[7]. The most frequent misdiagnosis in our series was mesenteric ischaemia. The median time elapsed between admission and operation ranges from 3 to 4·5 days[1,4,7,9,11] and was 2·5 days in our study. This should be attributed to delay in establishing the diagnosis and in stabilization of debilitated patients. Some patients refuse to undergo any surgery until the problem becomes more advanced, as in three of our cases.

Once a stone enters the gastrointestinal tract, it may be vomited, passed spontaneously, or become impacted. It is likely that more than 80 per cent of stones entering the gut through a biliary–enteric fistula will be uneventfully excreted[12]. However, spontaneous passage of an obstructing gallstone is exceptional[6–8,11]. Gallstones commonly impact in the ileum, the narrowest part of the small bowel where peristalsis is weaker than proximally[14,15]. In the present report, 73 per cent of the stones were impacted in the terminal ileum, a figure within the previously reported range of 50–75 per cent[1,2,6,9,11,12,17]. The proximal ileum and jejunum represent the second most frequent location accounting for 20–40 per cent of cases[1,5,12]. Stones in the duodenum represent less than 10 per cent of the total[3,7,9,11]. Colonic occlusion is rare but can occur with cholecystduodenal or cholecystcolonic fistula[1,2,7,8,29–32]. Like other authors[29,31], we found colonic obstruction involving only the sigmoid colon and exclusively in association with an underlying pathological narrowing, such as postdiverticulitis stenosis. It has been suggested that when the gallstone is very large, obstruction may occur without colonic abnormality, this being exclusively the result of a cholecystcolonic fistula[29,32]. Indeed it is difficult to conceive that a stone able to pass the ileocaecal valve would obstruct the large bowel.

The size of obstructing stones ranged in our series from 2 to 5 cm in their smallest diameter. Most reports indicate that stones smaller than 2·5 cm usually pass spontaneously[4,6,9], although smaller stones have caused fatal ileus[33], often associated with faecal impaction[7,11], and stones as large as 5 cm have passed spontaneously[9,14]. The size of stones mentioned in most previous reports concerned only their largest diameter; we feel that it is the smallest diameter that determines whether they will pass. Multiple stones are reported in 3–40 per cent of cases, and are often responsible for early recurrence[1,5–7,9,11,12,15,18]. They were noted in six of our patients. Faceted or cylindrical stones may indicate the presence of additional stones[1,11,34], and the entire gut should be palpated from the stomach through to the rectum.

Prompt relief of intestinal obstruction remains the cornerstone of management. Surgical intervention remains the treatment of choice in this setting, although there may be an as yet undefined group of patients in whom lithotripsy or endoscopy would be appropriate. Small bowel obstruction requires enterolithotomy with longitudinal incision placed on the antimesenteric border proximal to the site of impaction[7,15]. Careful closure of the enterolithotomy is needed to avoid narrowing of the intestinal lumen and we usually use a transverse closure for this reason. Bowel resection is sometimes necessary, particularly in the presence of a perforation. Manual expulsion of the stone through the caecum, although successful in one of our patients and in some previous case reports[1,7,16,17,35], should be used only in highly selected situations because of the danger of injury to mucosa[15] and undetected serous rupture of the bowel wall[1,2,7,8]. Similarly, attempts to crush the stone *in situ* can damage the bowel wall[1]. However, multiple stones can generally be extracted through a single incision by milking the gut and moving smaller stones towards bigger stones[12]. In sigmoid obstruction transanal delivery is rarely possible[1,5,29,31,35], although extraction by colonoscopy has been reported[36]. We feel that sigmoid resection removing the stone and the underlying stenosis is the treatment of choice. Some surgeons have successfully extracted the stone via a proximal colotomy without resection[29–32].

The main long-standing controversy in the management of gallstone ileus is whether biliary surgery should be carried out at the same time as the relief of obstruction of the gut (one-stage procedure), performed later (two-stage procedure) or not at all[37,38]. In the present series, mortality and morbidity rates due to non-biliary causes were comparable in the three treatment groups. Indeed, treatment of the biliary tract disease does not appear to increase the mortality rate, provided that patients are not shocked and have been fully resuscitated. However, of the 23 patients treated by enterolithotomy alone, 18 survived and ten developed biliary disorders; four had recurrent gallstone ileus, representing a 17 per cent incidence, which is more than the 5–10 per cent relapse rate generally reported[2,8,9,18,34,39]. Two other patients were rehospitalized for acute cholecystitis and one for acute cholangitis. Malabsorption and weight loss, although not present in this series, as well as acute cholangitis have been reported as the most frequent complications of residual fistulae[3,4,8,12,38]. Acute cholangitis, for instance, has been observed in 11 per cent of patients with cholecystduodenal fistula and 60 per cent with cholecystcolonic fistula[3,4,10,39]. The size of fistula has also been correlated with the risk of cholangitis[3]. Another major long-term complication of biliary–enteric fistula could possibly be gallbladder cancer[3,5,10,11,18,19]. In 57 patients undergoing surgery for such fistulae, Bossart *et al*. found an incidence of cancer of 15 per cent as opposed to 0·8 per cent among all patients having cholecystectomy[40]. Severe postoperative bleeding has also been described, generally arising from the erosion of a blood vessel during the passage of the gallstones[26,34,41], as was the case in one of our patients. Thus, there would seem to be some advantage, at least in terms of morbidity, in dealing with the biliary tract disease as part of the initial treatment.

Some authors have pointed out that a number of fistulae close spontaneously once the stone has passed, particularly when the cystic duct is patent or when there are no residual stones[1,4,9]. Other reports have substantiated this finding at subsequent cholecystectomy[4,18] and autopsy[42]. Similarly, ultrasonography and contrast gastrointestinal radiology enabled us to exclude residual fistulae or cholelithiasis in three asymptomatic patients who had been treated by enterolithotomy alone. Conversely, two of our patients who suffered from biliary symptoms had persistent fistulae, one of whom had cholelithiasis.

These results strongly suggest that the one-stage procedure is indicated when local and general conditions permit, unless it has been clearly demonstrated that no stones remain in the gallbladder. The preference for a two-stage procedure which might be suggested in this series (no deaths in six patients) should be modulated by the fact that two anaesthetics and longer hospital stay are required; the elderly often reject two consecutive operations. Nevertheless, when biliary surgery is not advisable at the initial operation, it appears justifiable to plan secondary elective fistula repair and cholecystectomy when there are biliary symptoms or residual cholelithiasis at ultrasonography.

Non-operative methods such as shock-wave lithotripsy and gallstone dissolution, or endoscopic sphincterotomy in cases of concurrent choledocholithiasis, should be considered in these elderly and high risk patients. Shock-wave lithotripsy may become the treatment of choice since evacuation of fragments might be facilitated by the fistula. However, as yet this method is untested under these conditions, and particular attention will have to be paid to the effect of shock waves in the presence of inflammation. On the other hand the fistula is a contraindication to the use of contact dissolution agents such as methyl ter-butyl ether, due to potential injury on the bowel mucosa. Finally, it seems reasonable to follow up asymptomatic patients treated by enterolithotomy who have no residual stones by serial ultrasonography.

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Management of the Mirizzi syndrome and the surgical implications of cholecystcholedochal fistula

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Several methods of handling the residual choledochal defects encountered during operation for type II Mirizzi syndrome have been described. Early experience with eight patients treated by a variety of procedures including direct suture and flap techniques led to disappointingly high morbidity and mortality rates. Since 1986 a standardized surgical approach has been used in four patients without complications or mortality. Essential to management are preoperative diagnosis by ultrasonography and endoscopic retrograde cholangiopancreatography and classification of the Mirizzi syndrome into two types as proposed by McSherry. Mirizzi type I consists of an extrinsic compression of the hepatic duct by a calculus impacted in the cystic duct or in Hartmann's pouch. This is treated by cholecystectomy with or without common bile duct exploration. In the more difficult Mirizzi type II, the stone has eroded into the hepatic duct causing a cholecystcholedochal fistula. This is treated by partial cholecystectomy and a cholecystcholedochoduodenostomy. This management strategy prevents inadvertent bile duct injury and has yielded satisfactory results.

Keywords: Mirizzi syndrome, gallbladder surgery, bile duct, fistula

In 1948 Mirizzi described a so-called functional hepatic syndrome in jaundiced patients[1] in which a calculus impacted in the cystic duct caused obstruction of the common hepatic duct by extrinsic compression. Although the syndrome is found in only 0·7–1·1 per cent of patients undergoing cholecystectomy[2–4], preoperative recognition and careful surgical management are essential because of the danger of bile duct injury.

McSherry in 1982 suggested a subclassification of the Mirizzi syndrome into two types based on endoscopic retrograde cholangiopancreatography (ERCP) findings[5]. Type I involves external compression of the common hepatic duct by a large stone impacted in the cystic duct or Hartmann's pouch. In type II, a cholecystcholedochal fistula is present, caused by a calculus which has eroded partly or completely into the common bile duct. The radiological features of the syndrome have been addressed in several recent small series[6–10], but the surgical implications of the presence (type II) or absence (type I) of cholecystcholedochal fistula have been underemphasized. In this report, we suggest a standardized surgical approach to the Mirizzi syndrome based on the McSherry classification, emphasizing the difficulties involved in repair of the residual choledochal defect in the type II situation.

Patients and methods

Between 1979 and 1988, 12 patients with the Mirizzi syndrome were encountered, representing approximately 1 per cent of all cholecystectomies performed in our clinic over this period. Five of these patients have been reported previously[3]. The average age was 73 years (range 45–87 years).

Before 1986 the preoperative diagnosis was made in three of the eight cases and no standardized surgical approach was used. Based on intraoperative findings, there were two examples of type I and six examples of type II Mirizzi syndrome.

After 1986, a systematic approach to diagnosis and operation was introduced. In the four most recently treated patients, the preoperative diagnosis was suspected on ultrasonography and confirmed by ERCP. Operation was performed 1 day after ERCP. Perioperative antibiotics (including antibiotic cover for ERCP) were administered for 24 h after operation or, in cases of cholangitis, for 5 days.

Surgical management since 1986 has emphasized minimal dissection in the region of Calot's triangle and the early intraoperative identification of the presence or absence of a cholecystcholedochal fistula. Choledochal defects were not directly closed; instead biliary–enteric reconstruction by cholecystcholedochoduodenostomy[11] was carried out. Frozen section of the excised portion of the gallbladder was obtained.

Results

The various procedures performed in eight cases managed before 1986 carried a disappointingly high morbidity rate, including pulmonary embolism, sepsis, multiorgan failure, pneumonia, haemorrhage and cholangitis. One patient died who developed biliary leakage after a gallbladder patch had been applied to the defect in the common hepatic duct.

The four patients treated since 1986 all had type II Mirizzi syndrome. A cholecystcholedochoduodenostomy was performed in three patients. In one elderly patient with poor general health, frozen section identified a gallbladder carcinoma. Anastomosis in this patient was considered unsafe and a T tube was inserted through the open gallbladder into the common hepatic duct and a silicone catheter was placed into the gallbladder neck. The postoperative course in all four patients was uneventful.

Discussion

The Mirizzi syndrome is a rare complication of long-standing gallstone disease currently more frequently identified using modern imaging techniques[4–10]. Ultrasound is the best screening method, with ERCP and/or percutaneous transhepatic cholangiography to confirm the diagnosis.

The risk of bile duct injury is increased in the Mirizzi syndrome. The shrunken gallbladder and Calot's triangle are involved in a severe inflammatory process with dense adhesions of oedematous tissues to the hepatoduodenal ligament. This distortion of the anatomy does not usually allow proper

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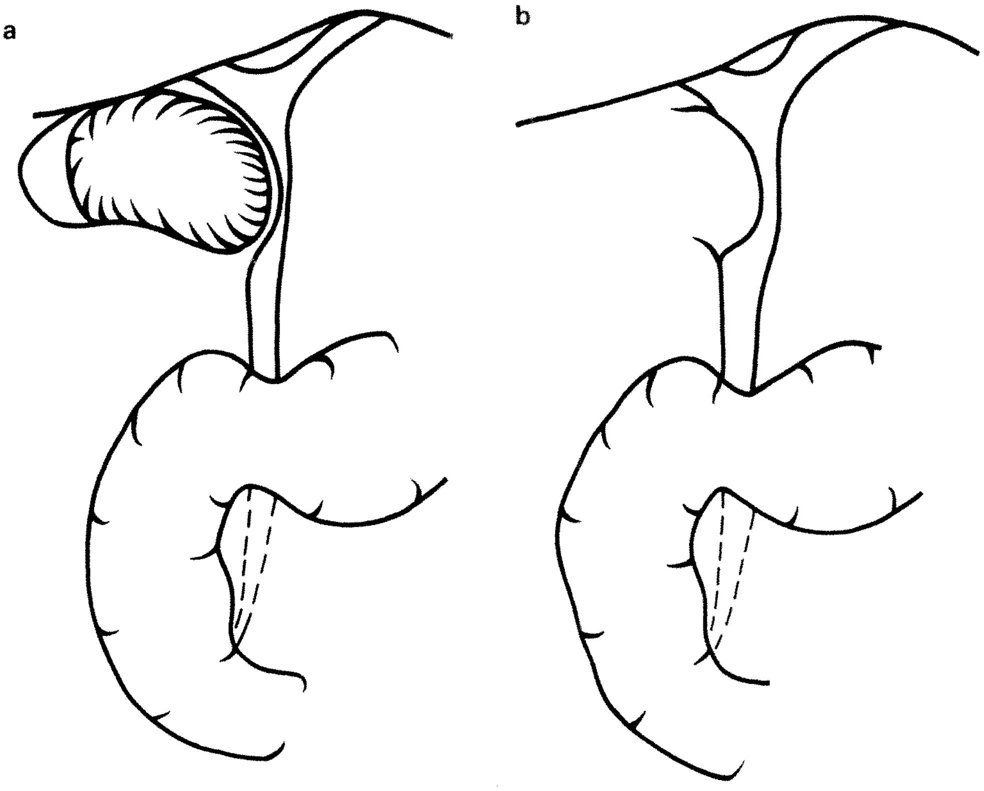

Figure 1 *Type I Mirizzi syndrome:* **a** *a stone impacted in the cystic duct or in Hartmann's pouch of the gallbladder causes jaundice of varying degree by a combination of compression of the common hepatic duct and the inflammation caused by the calculus; and* **b** *treatment consists of partial cholecystectomy. Routine common bile duct exploration is unnecessary and potentially dangerous*

dissection of the gallbladder. It is neither safe nor necessary to do so. Removal of the entire gallbladder bears a high risk of bile duct injury and the subsequent morbidity of bile duct repair[2]. Our policy is to define the two different types of Mirizzi syndrome and to employ a selective operative approach according to this classification.

Surgical approach

Rather than attempting to dissect the structures and risk bile duct injury, the initial step consists of incision of the gallbladder fundus and removal of the impacted stone. This manoeuvre enables the subtype of Mirizzi syndrome to be defined. A gush of bile into the opened gallbladder as the stone is removed indicates the presence of a fistula, since the cystic duct is always completely occluded as a result of the long-standing inflammatory reaction. Intraoperative cholangiography using a Foley catheter placed in the gallbladder neck may be used at this point to confirm the presence of a fistula. A frozen section is obtained to exclude gallbladder carcinoma. Subsequent surgical management is dictated by the presence or absence of cholecystcholedochal fistula.

Mirizzi type I

Two intraoperative objectives must be defined: the extent of cholecystectomy and the need for exploration of the common bile duct. In most cases partial cholecystectomy leaving the neck of the gallbladder in place is the more prudent approach (*Figure 1*); the cystic duct is always occluded as a result of the long-standing inflammation with fibrosis.

Common bile duct exploration should be performed only if the common bile duct is easily exposed; otherwise postoperative endoscopic sphincterotomy and stone extraction provide a safer alternative. Bile duct stenosis will generally resolve as the inflammatory response subsides following simple decompression by partial cholecystectomy. Postoperative interventions are seldom necessary with Mirizzi type I and these patients are often best served by simply removing the impacted gallbladder stone. If definitive management of associated pathology (common duct stones or stenosis) is thought necessary this is reassessed after resolution of the inflammatory process.

Mirizzi type II

The fistulous defect in Mirizzi type II is often of considerable size. Dissection of the neck of the gallbladder and common bile duct may enlarge this defect or result in bile duct transection. Various surgical methods for the management of the residual choledochal defect have been reported.

Our retrospective study, before 1986, showed that direct suture of the defect was associated with considerable morbidity. Simple suture of a longitudinal defect with or without a T tube is technically difficult. The use of part of the gallbladder wall as a free transplant cuff or a flap to cover the fistula has been suggested[3,4]. One of the patients in our pre-1986 series developed a biliary leak and ultimately died after such a procedure. The problems associated with direct repair probably occur because of the frequently associated bile duct stenosis which prevents healing unless diversion of the bile flow is achieved. Flap techniques use thickened tissue already damaged by the inflammatory process and the repair is therefore prone to failure.

For these reasons, we advocate biliary–enteric bypass to the wall of the cholecystcholedochal defect by either duodenostomy or Roux-en-Y jejunostomy. In our experience, cholecystcholedochoduodenostomy (*Figure 2*) has proved to be a safe and quick procedure. After mobilization of the duodenum a single layer, continuous anastomosis with Vicryl® (Ethicon Ltd., Edinburgh, UK) 4/0 suture is performed.

Tumours of the cystic duct occasionally mimic the Mirizzi syndrome[4,12] and in two patients we found gallbladder carcinoma occurring simultaneously with the Mirizzi syndrome. The age of these patients and their compromised general condition were considered contraindications to further

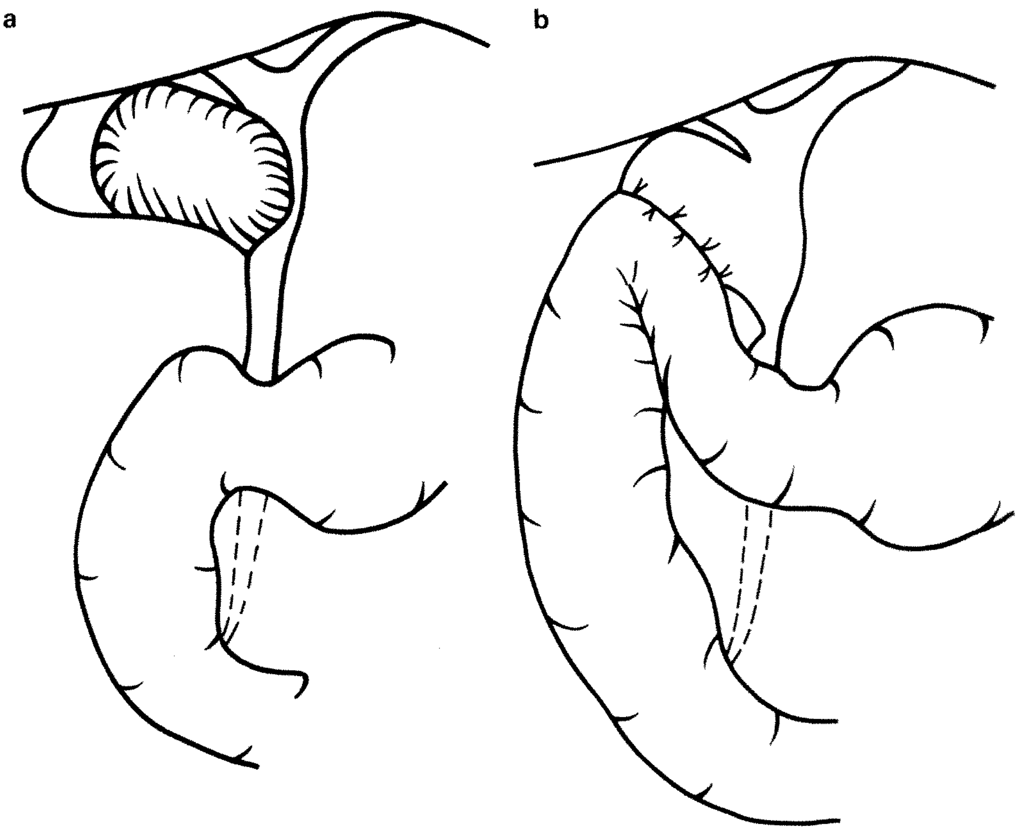

Figure 2 *Type II Mirizzi syndrome:* **a** *the calculus has protruded into the hepatic duct eroding the septum between the cystic and hepatic ducts and resulting in a cholecystcholedochal fistula; and* **b** *the cholecystcholedochal fistula is bypassed rather than directly closed. Cholecystcholedochoduodenostomy is the preferred method*

operative procedures. The identification of the gallbladder carcinoma was important for prognostic purposes.

In a young patient, when radical gallbladder resection for carcinoma may occasionally be contemplated, frozen section analysis is essential.

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Choice of incision and pain following gallbladder surgery

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A prospective randomized trial compared pain in the first 24 h after gallbladder surgery via an upper midline or a transverse incision. Pain was measured by the patients' self-administered consumption of pethidine, degree of postoperative respiratory impairment and a visual analogue pain scale. The upper midline incision group self-administered significantly more pethidine than the transverse incision group ($P<0{\cdot}001$)*, but there was no difference between the groups in respiratory function or visual analogue pain scale results 24 h after operation. Length of hospital stay was not different. An upper midline incision is more painful than a transverse incision in the first 24 h following gallbladder surgery.*

Keywords: Postoperative pain, patient controlled analgesia, gallbladder surgery, abdominal incisions

Many different incisions can be used for gallbladder surgery. Although the choice of incision is based primarily on the adequacy of access to the surgical field, other factors should also be considered among which postoperative pain and its sequelae are prominent. Incisions in the upper abdomen for gallbladder surgery can be broadly classified into vertical or horizontal types. The relative painfulness of these two groups of incisions has been assessed in the past, usually as one of a series of factors analysed. The results of these studies are contradictory[1–6]. The present prospective randomized trial was designed specifically to study postoperative pain in the first 24 h after gallbladder surgery via either an upper midline or a transverse incision.

Patients and methods

All patients gave informed consent to be included in the study which was approved by the local Ethics Committee. Sixty patients completed the study which contained only elective or semi-elective cases. Exclusion criteria were: a history of opiate abuse, opiates administered in the 24 h before operation, abnormal renal or hepatic function, or a surgeon's decision that the patient was inappropriate for inclusion in the trial. All patients were in category I, II or III of the American Society of Anesthetists description of physical status. Time from incision to closure was recorded for each patient. Length of incision and methods of closure were not standardized.

At the preoperative visit patients were instructed in the use of a patient controlled analgesia device, Pharmacia Deltec Model 5200 (Pharmacia (Australia) Pty Ltd., North Ryde, New South Wales, Australia). At the same time vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) were measured in the semirecumbent position using a spirometer, Vitalograph® (Vitalograph Ltd., Buckingham, UK). The best of three readings was recorded. *Table 1* shows the comparison of the two groups in terms of age, weight, height, sex and cigarette consumption.

After premedication with oral diazepam 10 mg, all patients received general anaesthesia (thiopentone induction, endotracheal intubation with suxamethonium, muscle relaxation with vecuronium and isoflurane/oxygen/nitrous oxide inhalation with mechanical ventilation). Intravenous pethidine 100 mg was administered to every patient during operation.

In the recovery ward the patient controlled analgesia device was connected to the intravenous line and was programmed to deliver pethidine 20 mg intravenously on each demand from the patient. There was no basal infusion of pethidine. There was a lockout period of 5 min after each demand; during this time further demands from the patient were ignored. A maximum dose of pethidine 100 mg in any 1 h was allowed and a non-return valve was inserted into the intravenous line to prevent reflux of pethidine into the maintenance infusion. Respiratory rate was measured hourly.

At 24 h after operation the patient was disconnected from the patient controlled analgesia device and the total self-administered dose recorded. If more than 20 min had elapsed since the last dose of opiate, spirometry was performed, using the same method as before operation, and a visual analogue pain scale was completed by the patient. The visual analogue pain scale consisted of a 10 cm line, one end of which represented 'no pain' and the other 'worst pain imaginable'. The patient was asked to make a mark on the line to indicate the severity of his pain. Length of stay in hospital was tabulated for each patient.

Statistical analysis was done using a biomedical data analysis package[7]. Student's t test or χ^2 analysis was used where appropriate. $P=0{\cdot}05$ was accepted as significant.

Results

One patient died of a pulmonary embolus at 30 h after operation. His data were included in the analysis except for length of hospital stay. Two patients were excluded from the trial after randomization, one because of inability to master the use of the patient controlled analgesia device and the other because the surgeon considered inclusion inappropriate.

Duration of operation

Duration of operation was similar in both groups. The mean(s.e.m.) in the upper midline incision group was 51·9(3·3) min, and in the transverse incision group it was 60·4(3·9) min ($P=0{\cdot}10$).

Table 1 *Comparison of the groups*

	Upper midline incision ($n=31$)	Transverse incision ($n=29$)	Statistics and P values
Age (years)	54·0(2·8)	57·1(2·6)	$t=-0{\cdot}82$, d.f. = 58, $P=0{\cdot}42$
Weight (kg)	69·4(2·2)	70·6(2·9)	$t=-0{\cdot}37$, d.f. = 58, $P=0{\cdot}71$
Height (cm)	165·8(1·59)	167·0(1·88)	$t=-0{\cdot}53$, d.f. = 58, $P=0{\cdot}60$
Sex (M/F)	10/21	12/17	$\chi^2=0{\cdot}54$, d.f. = 1, $P=0{\cdot}46$
Smokers/ non-smokers	8/23	3/26	$\chi^2=2{\cdot}39$, d.f. = 1, $P=0{\cdot}12$

Values are expressed as mean(s.e.m.). t, Student's t test; d.f., degrees of freedom; χ^2, χ^2 analysis

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Table 2 *Preoperative spirometry results in patients about to have gallbladder surgery*

	Upper midline incision ($n=31$)	Transverse incision ($n=29$)	Statistics and P values
FEV_1 (ml)	2465(160)	2455(148)	$t=0{\cdot}05$, d.f. $=58$, $P=0{\cdot}96$
VC (ml)	3150(168)	3158(167)	$t=-0{\cdot}03$, d.f. $=58$, $P=0{\cdot}97$

Values are expressed as mean(s.e.m.). FEV_1, forced expiratory volume in 1 s; VC, vital capacity; t, Student's t test; d.f., degrees of freedom

Table 3 *Postoperative spirometry results in patients after gallbladder surgery*

	Upper midline incision ($n=31$)	Transverse incision ($n=29$)	Statistics and P values
*Percent FEV_1	48·3(3·04)	55·4(2·81)	$t=-1{\cdot}72$, d.f. $=58$, $P=0{\cdot}09$
†Percent VC	49·1(2·78)	54·2(3·07)	$t=-1{\cdot}24$, d.f. $=58$, $P=0{\cdot}22$

Values are expressed as mean(s.e.m.). t, Student's t test; d.f., degrees of freedom

$$\text{*Percent } FEV_1 = \frac{\text{Postoperative } FEV_1}{\text{Preoperative } FEV_1} \times 100$$

$$\text{†Percent VC} = \frac{\text{Postoperative VC}}{\text{Preoperative VC}} \times 100$$

Pethidine consumption

The mean(s.e.m.) pethidine dose for the upper midline group was 550(34·3) mg, and for the transverse group it was 370(30·2) mg ($P<0{\cdot}001$).

Pulmonary function

Preoperative spirometry (FEV_1/VC) was similar in both groups (*Table 2*). The values were within the normal range when expressed as a mean and corrected for age, sex and height.

Pulmonary function 24 h after operation was similarly depressed in both groups. Postoperative VC and FEV_1 were expressed as a percentage of the preoperative value (*Table 3*).

Visual analogue pain scale

There was no statistically significant difference in the visual analogue pain scale results between groups. The mean(s.e.m.) score in the upper midline incision group was 3·65(0·42) while in the transverse incision group it was 3·51(0·39) ($P=0{\cdot}81$).

Length of hospital stay

There was no statistically significant difference in length of hospital stay between groups. In the upper midline incision group the mean(s.e.m.) length of hospital stay was 6·3(0·4) days and in the transverse incision group it was 7·0(0·6) days ($P=0{\cdot}22$).

Discussion

Pain and its consequences have been studied with specific reference to the type of incision used for gallbladder surgery. To the authors' knowledge this is the first study using self-administered opiate consumption as a measure of the relative painfulness of surgical incisions. In previous work comparing incisions for upper abdominal surgery, pain was only one of many factors studied and was measured by adding the amount of intramuscular opiate administered by hospital staff[1,2,4]. As Greenhall *et al.*[2] suggest, these were fruitless exercises because the amount of opiate dispensed probably depended more on local ward practices than the amount of pain actually suffered. In any event there was little difference demonstrated between groups with different incisions.

In the present study, by contrast, the upper midline incision group self-administered significantly more pethidine than the transverse incision group. It may be deduced that an upper midline incision is more painful than a transverse incision in the first 24 h after gallbladder surgery. Furthermore, in future studies the consumption of intravenous opiate, delivered via an accurate patient controlled analgesia device, should give a reliable and reproducible measure of postoperative pain.

All upper abdominal incisions produce a profound reduction in ventilatory capacity[1–6], but whether the type of incision affects the degree of reduction remains unclear. Several studies suggest that transverse incisions cause less reduction in VC and FEV_1[1,3,7,8,9] but others have found no difference in this respect[2,5,6]. In these studies intramuscular opiate was administered as deemed necessary by hospital staff, whereas in the present study patients themselves were given control of their analgesia. This is a crucial factor when assessing the reduction in respiratory function following abdominal surgery. Present data show no significant difference between upper midline and transverse incision groups in FEV_1 and VC at 24 h after operation. Therefore, it seems that given sufficient analgesia, respiratory function is similarly impaired by both upper midline and transverse incisions for gallbladder surgery.

The visual analogue pain scale is an accepted and proven method of assessing the degree of pain a patient suffers[10,11]. The visual analogue pain scale results were not statistically different between groups, attesting to the good sense of patients in that they self-administered enough pethidine to control their pain to their satisfaction. The difference between the groups lay in the amount of pethidine required to achieve this pain score.

Length of hospital stay was chosen as a crude measure of morbidity and there was no significant difference between groups. This contrasts with other studies favouring subcostal incisions in which patients were examined for at least 7 days after operation[1,4]. In the present study 20 per cent of patients were discharged within 4 days of surgery and approximately 50 per cent within 6 days. This suggests that the long postoperative stays of some other studies were due to local practice or to some patients being kept in hospital solely for the purposes of the study.

In summary, the present work has shown that upper midline incisions were more painful than transverse incisions in the first 24 h after operation. The type of incision did not affect the degree of postoperative respiratory impairment, visual analogue pain scale results or length of stay in hospital.

Acknowledgements

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Symposium at the International Federation of Surgical Colleges Meeting, September 1989

Impact of AIDS on surgery

At the International Federation of Surgical Colleges Meeting in September 1989, a symposium was held with the objective of informing an international audience of surgeons about the scourge and epidemic of acquired immune deficiency syndrome (AIDS) which is now affecting all countries and is truly a pandemic disease. AIDS was first recognized among the homosexual community in the USA in 1980 though it has been recognized in Africa since the late 1960s. On the 31st August, 1989, 177965 cases of AIDS have been officially reported to the World Health Organization. This almost certainly represents under-reporting or under-diagnosis; the true figure is probably nearer 300000. The number of reported AIDS patients is misleading because most are without symptoms for some 4–5 years after the initial infection. For every symptomatic case of AIDS there are 25–30 people infected and asymptomatic. Fear and ignorance of AIDS is a big problem. The estimated cost of treatment per patient is between $25000 US and $150000 US. In most developing countries the per capita health budget is only $2.00 US so this has an enormous cost impact on the less affluent emerging nations.

The symposium covered the problems surgeons face treating patients already infected with human immunodeficiency virus (HIV). One of the immediate hazards is that many seropositive patients, though infectious, are in an asymptomatic state before clinical manifestations appear; hence the potential danger for surgeons and other health personnel. The question is whether all surgical patients should be tested routinely which was the accepted practice in sexually transmitted disease, for example, syphilis. The overriding right of the patient to privacy and confidentiality with the necessity of a signed form of consent before any procedure such as blood testing for HIV antibodies is accepted practice nowadays. Routine testing without the patient's consent is currently held to be neither ethical nor acceptable. However, if the patient has these rights, then it is arguable that so has the surgeon in order to protect himself and his staff. Most AIDS victims, on the other hand, readily admit to having the disease so we should make great efforts to persuade patients to have voluntary testing. Apart from the advantages to the health staff knowing of the hazards involved, routine testing would give more epidemiological information. AIDS is quite uniquely the first 'protected' epidemic in modern history, though in many countries it is a notifiable or at least a reportable disease. Although AIDS is notifiable or at least reportable in some countries, the patient should not be identified.

It seems generally agreed that it is unethical for a surgeon to deny operation to a patient who is HIV-positive and there is circumstantial evidence that in some places in the United States he or she could lose the licence to practice by such refusal. There is no right, however, to enforce needless risks on those who come into contact with an infected patient but, if normal precautions are taken by surgeons and health staff, the risk is very low, well below 0·5 per cent. This is in contrast to hepatitis B virus infection, which is 20 or 30 times more infectious, but of course less likely to cause a fatal outcome. In the past 7 years only 18 cases of health workers being infected by patients with AIDS have been recorded. Worldwide, there have been some 20 workplace infections from needlesticks and exposure to secretions.

In the absence of routine testing for HIV infection all patients who undergo surgery should be regarded as potentially HIV-positive and precautions should be taken to avoid direct contact with their secretions, blood or open skin lesions. Needlestick injuries or splashes of infected blood on the open skin are the commonest way of picking up the infection outside sexual activity. Surgeons should meticulously observe established aseptic techniques, avoid puncturing gloves (nearly 50 per cent of gloves are punctured during operations) and be extra careful to avoid self-inflicted injury with sharp instruments and needles. Bleach solution 1:10 is useful to decontaminate secretion spillage. HIV is heat sensitive and easily destroyed by heat and most disinfectants. Good operating room standards will protect the staff from the infection.

What happens if the surgeon is contaminated either by a patient with known HIV infection or an unsuspected HIV carrier? The contaminated site should be promptly cleansed with alcohol or iodine. Human T-cell lymphotrophic virus (HTLV-3) antibody testing should be performed and she/he should be kept out of the theatre. If the test is negative, it should be repeated in 6 weeks and then at 3, 6 and 12 months after exposure. Counselling is important and azido guanosine thymidine (AZT) prophylactic treatment should be offered.

HIV infection poses a special problem in African countries and as many as 20 per cent to 30 per cent of the population may be HIV-positive. The clinical presentation there differs from that reported in Western countries, not only in a higher incidence, but in the appearance of new presentations and behaviour of old diseases with new pathologies such as: Kaposi's sarcoma, tumours of the pharynx, cervix and Burkitt's lymphoma; manifestations of surgical tuberculosis of the spine, joints and lymph nodes; impaired would healing and increased incidence of sepeis; and some unusual vascular manifestations. These clinical manifestations present new diagnostic and management problems and call for careful epidemiological studies as well as measures to cope with the increased use of scarce hospital resources in countries already experiencing a crisis in health care provision.

Biological medical sciences have been very successful in identifying the cause of this disease. Apart from a cure, which no doubt will come in time, we are all striving for control of the disease. This will depend on the success of the social services and more controlled sexual behaviour. The challenge is of a social nature, of risky sexual behaviour and how to modify it.

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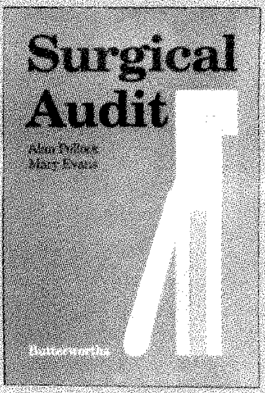

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Truncoumbilical bypass of the portal vein in radical resection of biliary tract tumour involving the hepatic duct confluence

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Before combined resection of the right hepatic lobe and the hepatoduodenal ligament, an autogenous external iliac vein was interposed between the root of the portal vein trunk and the umbilical portion of the vein in four patients with biliary tract tumour. The left hepatic arterial pathway was preserved, except in one case in whom resection of this artery was followed by reconstruction. This procedure allowed successful and safe extended right hepatic lobe resection and combined en bloc *resection of the hepatoduodenal ligament while preserving hepatic blood perfusion.*

Keywords: Biliary tract cancer, radical resection, portal vein bypass, hepatoduodenal ligament

Results of treatment of hilar cholangiocarcinoma and gallbladder cancer continue to be poor, in part, because of the low resectability rates. Difficulties in diagnosis and the complicated anatomical location of the tumour have compounded the problem of management and reduce the prospect of surgical cure. The complicated anatomical location has evoked interest in new approaches, as evidenced by advocacy of extensive resection[1–5], which includes resection of the liver, hepatoduodenal ligament and pancreatic head with reconstruction of the resected vital vessels. In operations on four patients with tumour of these parts, we found that a prior bypass graft made between the umbilical portion of the portal vein and its root permitted successful extended hepatic right lobectomy in combination with total resection of the hepatoduodenal ligament. The innovative technique devised for this bypass and the problems involved are presented here.

Patients and methods

From January 1985 to March 1988, 40 patients with advanced biliary tract cancer were treated. Of these, 14 had gallbladder cancer and 26 ductal cholangiocarcinoma. The cholangiocarcinomas of all 26 patients with ductal cancer had infiltrated the hepatic hilus. Four cases (all men with an age range of 33–76 years), in whom intraoperative indications were satisfied (see below) underwent combined resection of hepatic segments (1, 5–8 and a part of 4) and the hepatoduodenal ligament after truncoumbilical bypass of the portal vein. In three cases percutaneous transhepatic biliary drainage had been performed in the referring institution and their serum total bilirubin values had fallen from 145–296 μmol/l to 21–31 μmol/l in 6–9 weeks.

Operative technique

Confirmation of indications. After laparotomy, ultrasonography was used to decide whether the hepatic lateral segment was intact and well developed, and to check that the umbilical portion of the portal vein had not been infiltrated. In addition, it was confirmed that the patent portal vein trunk was accessible at the upper edge of the pancreas.

Preparation of autogenous vein graft. An extraperitoneal approach through an oblique incision in the lower right abdomen allowed excision of the right external iliac vein. Turning the graft inside out, its valves were removed.

Anastomosis of the bypass graft. The umbilical portion of the portal vein was side clamped and incised longitudinally for more than 15 mm, and an obliquely cut end of the vein graft was anastomosed to the incision in end-to-side fashion (*Figure 1*). After shifting the clamp to the anastomosed end, the other obliquely cut end of the graft was anastomosed end-to-side to the portal vein trunk at its confluence with the splenic vein. The portal vein beyond the anastomosis then was severed obliquely and its cut end sutured, although in one case it was ligated contiguous to the anastomosis and then severed. In another patient the portal vein trunk was first severed at the root, after which the graft and distal portion of the portal trunk were anastomosed end-to-end with a carotid shunt tube[6].

Dissection of the main hepatic artery. Generally, the main hepatic artery was elongated and therefore easily dissected from the hepatoduodenal ligament. When possible the main hepatic artery and left hepatic artery were preserved, although in one case with infiltration of the artery the vessels were severed and reconstructed by interposing an autogenous saphenous vein graft.

En bloc *resection.* Subsequently, hepatic segments 1, 5–8 and the inferior part of segment 4 were resected together with the hepatoduodenal ligament and the regional lymphatic tissue (*Figure 2*). Haemorrhage during parenchymal dissection was controlled when necessary by encircling segment 4 with a rubber tube (8 mm in diameter) which crossed the transverse portion of the portal vein close to the umbilical anastomosis.

Reconstruction of the hepatic duct. The last step was reconstruction of the hepatic duct by the Roux-en-Y method. When tumour has

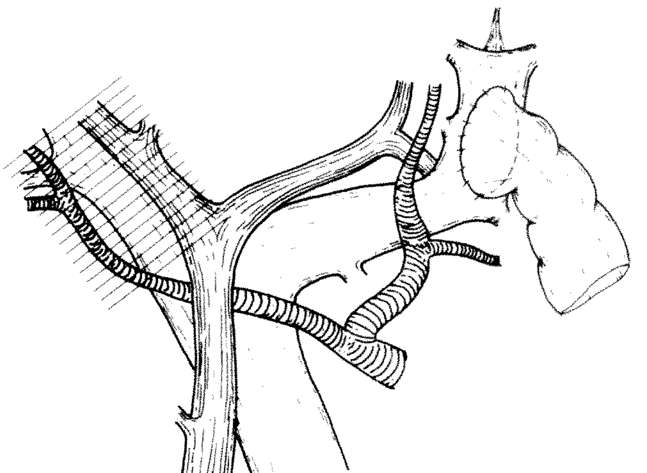

Figure 1 *Illustration of the anastomosis of the graft. The graft was anastomosed end-to-side with the umbilical portion. Diagonal lines indicate infiltration of tumour*

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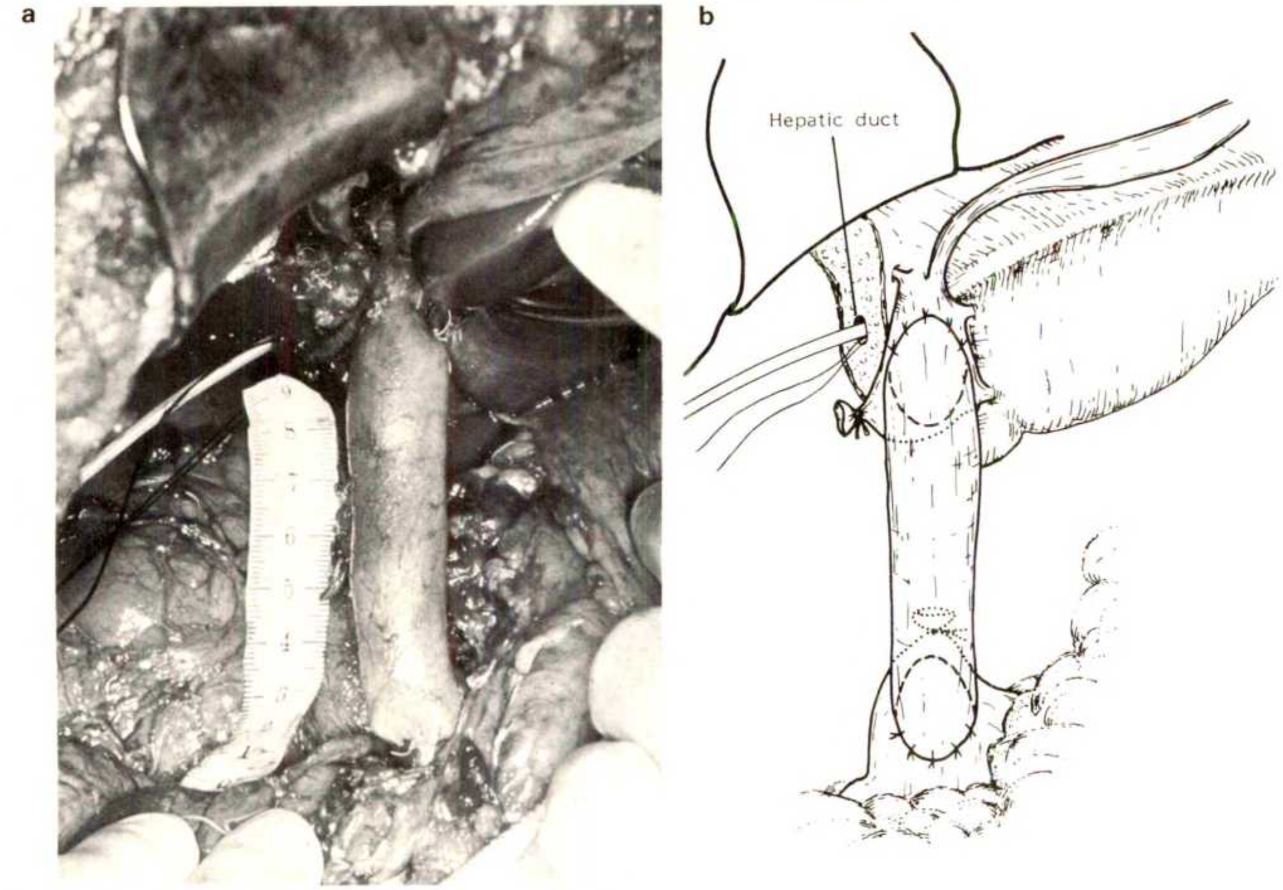

Figure 2 *Photograph* **a** *and diagram* **b** *showing an implanted graph*

invaded such contiguous tissues as the pancreas, duodenum and colon, appropriate resection is undertaken before making the bypass graft.

Case reports

Case 1. A 76-year-old man experienced jaundice with episodes of fever. In January 1987 the confluence of his hepatic ducts was found to be obstructed by cholangiocarcinoma. He was admitted to hospital for surgery in April. The tumour had infiltrated the right hepatic duct to its confluence and portal bifurcation. Anastomosis between the graft and the portal vein trunk was performed end-to-end. Operation time was 10 h and the blood loss was 2295 ml. The postoperative course was uneventful, his transaminase levels returning to normal in 10 days. His maximal serum total bilirubin concentration was 43 μmol/l, but after 3 weeks this value had decreased to normal. The patency of the graft was demonstrated by digital subtraction angiography after 5 weeks (*Figure 3*). Flow through the reconstructed portal vein was 500 ml/min during the operation as measured by the beam transit time technique, and 1072 ml/min 5 weeks after as measured by Doppler flowmetry. Eight months after the operation ultrasonography and blood parameters demonstrated graft patency. The patient died of recurrence 14 months after the operation.

Case 2. A 34-year-old man presented with general malaise and jaundice. Complete obstruction of his bile ducts from the posterior inferior branch to the confluence indicated cholangiocarcinoma. Angiography revealed apparent infiltration of the bifurcation of his portal vein and the hepatic artery (branching from the superior mesenteric artery) was also infiltrated. Laparotomy showed a huge solid tumour infiltrating the right hemicolon, the proximal half of the pancreas with the duodenal loop, the hepatoduodenal ligament and the liver. Although disseminated solid nodules were seen on the mesocolon adjacent to the tumour, peroperative histological examination of the para-aortic lymph nodes revealed no malignancy. After transection of transverse colon, terminal ileum, stomach, duodenum and pancreatic body, the venous bypass procedure was performed. During *en bloc* resection including the hepatic artery the bypass became thrombosed, but patency was immediately restored by thrombectomy. Hepatic segments 1, 5–8 and the medial inferior part of segment 4 were resected. Operation time was 18 h and peroperative blood loss was 4760 ml. The postoperative course was uneventful.

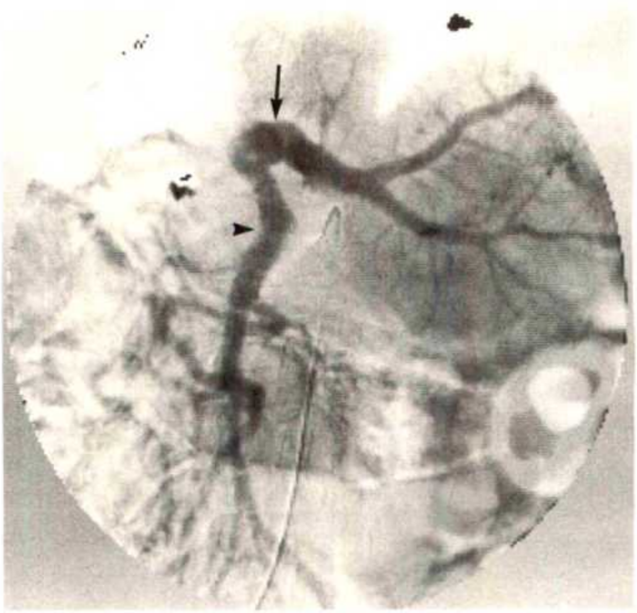

Figure 3 *Postoperative digital subtraction angiography in case 1. Arrow, umbilical portion; arrowhead, distal end of the graft*

Histology of the resected specimen did not reveal malignancy (in the other cases, adenocarcinoma was proved) and he was free of disease with the patent portal graft after 20 months of close follow-up.

Case 3. A 56-year-old man presented with jaundice. The confluence of his hepatic ducts was stenosed by cholangiocarcinoma. The portal vein from the right branch to the bifurcation appeared to be infiltrated. Taking 8 h and leading to loss of 4300 ml of blood, operation was performed by the present procedure and hepatic segments 1 and 5–8 were resected. Doppler flowmetry 5 months after operation revealed that the blood flow in the portal vein was 928 ml/min and in the superior mesenteric vein it was 500 ml/min Graft patency was demonstrated by superior mesenteric arteriography after 3 weeks and by magnetic resonance imaging after 6 months He stayed in the hospital for 7 weeks after operation because of subdiaphragmatic abscess contiguous to the raw surface of the liver. He appeared to be healthy after 7 months, but he was later admitted to his village clinic with sepsis probably caused by the recurrent abscess; he died suddenly from massive haematemesis 8 months after operation.

Case 4 A 33-year-old man entered hospital with epigastric pain. Examination revealed gallbladder cancer with prominent infiltration of the hepatoduodenal ligament The right hepatic artery was tightly encased. The right branch of the portal vein was compressed markedly and its trunk obstructed almost completely. Using the present procedure we performed *en bloc* resection including hepatic segments 1, 5–8 and the inferior part of segment 4. Operation time was 14 h and blood loss was 5000 ml. The resected specimen revealed protrusion of the tumour into the lumen of the common bile duct and portal trunk. The postoperative course was uneventful The patency of the graft was demonstrated after 12 months by computed tomography and ultrasonography. The patient is still alive after 17 months.

Discussion

The main purpose of our procedure is to ensure portal flow to the liver remnant before combined resection of the hepatic lobes and hepatoduodenal ligament. Hitherto, temporary interruption of the portal flow has been required when performing such combined resection Occlusion of the portal flow during the operation is said to involve few risks[7], but it seems best to avoid even temporary interruption of this flow Gross congestion of the intestine after portal interruption leads to third space fluid sequestration and other unfavourable events which may increase the risk of death during extensive hepatic resection[8] Tsuzuki *et al.*[9] reported such a fatality in the combined resection of the hepatic lobe with the bile duct and portal vein in jaundiced patients. Moreover, the liver is sensitive to the simultaneous occlusion of the portal vein and hepatic artery for more than 15 min[10], a situation which might occur during portal occlusion in conjunction with obstructive infiltration of the artery or during complete resection of the hepatoduodenal ligament. We therefore believe that maintenance of the portal blood flow with no temporary interruption is an important factor in lowering operative risk.

Without a prior bypass, maintenance of the portal flow is only possible by the direct insertion of a cannula (such as a carotid shunt tube) between both cut ends, but this difficult practice cannot be recommended. The present bypass procedure employs autogenous right iliac vein. We have used this vein in 34 mesocaval H shunt operations. The mean diameter of this graft was 10 mm and its length 90 mm. Of veins of this size, the external iliac vein is the most easily obtained. Follow-up (4–9 years) of 17 of our 34 patients revealed that only two had experienced a dull aching sensation in the leg, despite enlargement of the right leg in all 17. In the four graft cases reported here, no unfavourable complaints were noted.

The approach to the umbilical portion of the portal vein is simple. The parenchymal bridge that sometimes covers this section of vein was not present in our four patients Our preliminary results with the technique appear favourable and the operative risk of the procedure does not seem to be high Long-term follow-up of a large number of cases is planned to ascertain the value of this procedure.

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Reduced water and sodium intakes associated with high levels of natriuretic factor following common bile duct ligation in the rabbit

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Renal failure complicating obstructive jaundice (OJ) is probably linked to reduction of the extracellular water compartment. To elucidate the mechanism by which OJ leads to isotonic water depletion we studied a group of rabbits with OJ after common bile duct ligation (n = *17) and another group of sham operated rabbits* (n = *14) for 10 days. Water intake and balance for two study periods (1–4 and 7–10 days after operation) were calculated. Renal function, sodium balance and plasma atrial natriuretic factor were determined on the fourth and tenth days after operation. Water intake and balance were lower in the OJ group both in the first study period (230* versus *519 ml/days 1–4,* $P < 0.001$*; and* −*2·4* versus *219 ml/days 1–4,* $P < 0.0001$ *respectively) and in the second study period (260* versus *865 ml/days 7–10,* $P < 0.0001$*; and 11* versus *379 ml/days 7–10,* $P < 0.0001$ *respectively). Sodium intake was negligible in the OJ group both on day four (0·73* versus *7·15* mM*/24 h,* $P < 0.0001$*) and on day 10 (0·78* versus *15·78* mM*/24 h,* $P < 0.0001$*). As a result plasma osmolality did not change. Day 10 urine osmolality and osmolar clearance were reduced in the OJ group (653* versus *1103 mOsm/kg,* $P < 0.0001$ *and 0·09* versus *0·25 ml/min,* $P < 0.0001$ *respectively) together with a decreased creatinine clearance (3* versus *11 ml/min,* $P < 0.0001$*). Atrial natriuretic factor was increased in jaundiced rabbits (day 4, 22·7* versus *7·5 fmol/ml,* $P < 0.0001$*; and day 10, 26·5* versus *11·2 fmol/ml,* $P < 0.02$*). These findings suggest that OJ leads to an isotonic volume depletion resulting from abnormalities of the extracellular volume regulating mechanisms. These appear to be secondary to an inappropriate elevation of the atrial natriuretic factor plasma concentration.*

Keywords: Obstructive jaundice, natriuretic factor

The causes of renal dysfunction in obstructive jaundice (OJ) have not been clearly elucidated. Empirical perioperative treatment with mannitol to prevent renal function deterioration has failed to show any benefit[1] and there is a need to gain further insight into the mechanisms of renal changes associated with bile duct obstruction. Using a multi-isotope dilution technique in an animal model[2] the authors have observed that 12 days after ligation of the common bile duct there is a 35 per cent reduction of the extracellular fluid compartment. Other authors have also made observations consistent with the existence of contracted extracellular water and plasma volumes in OJ[3–7]. The cause is not known although Levy and Finestone[6] have demonstrated that acute obstruction of the common bile duct in the dog is immediately followed by a humorally mediated increase in diuresis and natriuresis. The present investigation was undertaken to examine the mechanisms leading to water and sodium depletion in OJ. Specifically, spontaneous water intake and balance, renal concentrating ability and plasma levels of atrial natriuretic factor (ANF) were studied after common bile duct ligation in the rabbit.

Materials and methods

Thirty-one New Zealand rabbits of body-weight ranging between 2500 and 3000 g were used. The animals were divided into two groups: an OJ group ($n = 17$) was submitted to common bile duct ligation, and a sham operated (SO) group ($n = 14$) to a sham operation. The animals were kept in metabolic cages from 4 days before operation (to allow for adaptation) until the end of the study 10 days after laparotomy. Water and chow (Panlab, Barcelona, Spain, 3·1 mg of sodium/g of chow) were offered *ad libitum* to both groups of animals. After surgery, body-weight, water intake and diuresis were recorded daily. Cumulative water balance uncorrected for extrarenal losses (intake minus output of urine) was calculated for two postoperative periods: days 1–4 and days 7–10. Sodium balance uncorrected for extrarenal losses was calculated on days 4 and 10. Six rabbits in the OJ group and seven in the SO group were provided with indwelling internal jugular catheters to allow atraumatic blood sampling with minimal stress for ANF measurements. In all animals, blood (through jugular catheter or middle ear artery) and urine samples were obtained on days 4 and 10 for renal function and ANF measurements. When the study was completed the animals were sacrified and a post mortem performed to check for bile duct dilation in the OJ group and to rule out ascites or other intrabdominal complications.

OJ was produced by surgical ligation of the common bile duct. Intramuscular ketamine (75 mg) was used for anaesthetic induction and 1–2 per cent Halothene® (Hoechst, San Felin Llobregat, Spain) for maintenance. Through a median laparotomy the common bile duct was dissected free in all animals and doubly ligated with 3–0 silk. Internal jugular vein catheterization was then carried out through a lateral 2 cm neck incision in the appropriate animals using a 7 cm polyethylene 14 French gauge catheter. The catheter was tunnelled and brought out in the interscapular region where it was locked and kept patent with heparinized saline. Antibiotic prophylaxis (cefonicid, Smith Kline and French, Madrid, Spain, 125 mg/day intramuscularly) was

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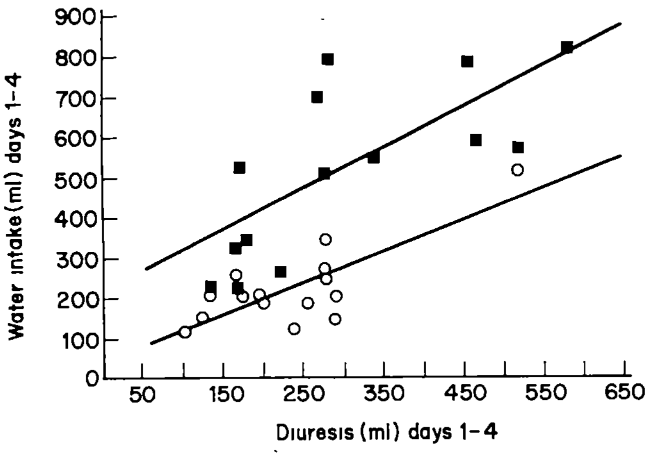

Figure 1 *Correlation between diuresis and water intake during the first 4 days after common bile duct ligation,* ○; *(r = 0·76), and sham operation,* ■, *(r = 0·71) In both groups, correlation was highly significant (P < 0·001)*

given during the first 3 days of the experiment. Creatinine and bilirubin were measured in a Technicon® (Technicon Instruments Corporation, Tarrytown, New York, USA) autoanalyser. Plasma and urine sodium were measured by flame spectrophotometry. Osmolality was calculated by the decrease in plasma freezing temperature Calculations of clearances were done using standardized formulae ANF was determined by radioimmunoassay. Plasma samples were analysed after extraction on C18 Sep-Pack® cartridges (Waters Associates, Milford, Massachusetts, USA) as previously described[8] Extraction recovery in individual samples was estimated by the addition of 125I-α-h ANF (approximately 500 counts per min) with a mean(s.d.) of 73(6) per cent. The assay was performed by the equilibrium method. Synthetic α-rat ANF (Bachem Incorporated, Torrance, California, USA) was used as standard 125I-α-h ANF and antiserum to α-ANF were obtained from Amersham International, Amersham, UK. Separation of antibody bound and free fractions of the peptide was performed by adding 300 μl charcoal-dextran suspension. The mixture was thoroughly mixed and centrifuged (15 min at 300g) Activity of supernatant was determined in a γ-counter Results were corrected for extraction recovery Inter- and intra-assay coefficients of variation were 15·1 per cent and 10·0 per cent respectively

Data have been processed with a Macintosh II® (Apple Computer Incorporated, Cupertino, Californa, USA) computer using the Statview® (Abacus Concepts Incorporated, Berkeley, California, USA) statistical package An unpaired, two tailed, Student's *t* test was used to compare both groups only if the requirements for this test were met For non-parametric data distribution the Mann–Whitney *U* test was used Results are expressed as mean(s d).

Results

Balance studies

The percentage loss of body-weight was greater in the OJ group both on the fourth (11(2) *versus* 3(3) per cent, $P < 0{\cdot}0001$) and the tenth (24(19) *versus* 3(8) per cent, $P < 0{\cdot}001$) day after operation. Water intake during the first plus the second study periods was lower in the OJ group (490(224) *versus* 1385(445) ml/days 1–4, $P < 0{\cdot}0001$). In both groups a close correlation was found between water intake and diuresis; data corresponding to the first period are shown in *Figure 1* Correlation was even closer during the second period ($r = 0{\cdot}91$ for the OJ group and $r = 0{\cdot}88$ for the SO group). However, the regression lines were quite different and, as can be derived from *Figure 1*, for a given water intake diuresis was much higher in the OJ group than in the SO group Water balance calculated without subtracting extrarenal losses was lower in the OJ group both in the first (−2·4 *versus* 219 ml/days 1–4, $P < 0{\cdot}0001$) and in the second (11 *versus* 379 ml/days 7–10, $P < 0{\cdot}0001$) study periods. Sodium intake on the fourth and tenth days was lower in the OJ group (0·73(0·2) *versus* 7·15(1·7) mM, $P < 0{\cdot}0001$ and 0·78(0·3) *versus* 15·78(4·8) mM, $P < 0{\cdot}0001$ respectively) There was a strong positive correlation between sodium intake and sodium urinary excretion in the SO group both on the fourth ($r = 0{\cdot}87$, $P < 0{\cdot}005$) and the tenth ($r = 0{\cdot}90$, $P < 0{\cdot}0001$) days but this was lost in jaundiced animals.

Renal function studies

Results of renal function studies are shown in *Tables 1* and *2*. On day 10 the OJ group showed a significantly decreased creatinine clearance together with an impairment of renal concentration ability shown by a decreased urine osmolality and osmolar clearance in spite of a markedly reduced water intake. Renal sodium excretion was lower in the OJ group but, if we take into account the extremely reduced sodium intake, jaundiced animals were in a negative whereas SO animals were in a positive sodium balance.

ANF determinations

Plasma concentration of ANF was higher in the OJ group both on the fourth (7·5(5·1) *versus* 22·7(3·2) fmol/l, $P < 0{\cdot}0001$) and the tenth (11·2(7·7) *versus* 26·5(9·8) fmol/l, $P < 0{\cdot}02$) days after bile duct ligation. In the 13 rabbits of both groups in which ANF was measured, it correlated inversely with sodium intake in the two periods ($r = -0{\cdot}80$, $P < 0{\cdot}003$ and $r = -0{\cdot}70$, $P < 0{\cdot}02$; *Figures 2* and *3*) and with water intake on the fourth day ($r = -0{\cdot}80$, $P < 0{\cdot}001$, *Figure 4*).

Discussion

These data indicate that after common bile duct ligation, jaundiced animals lose an appreciable amount of weight mainly because they fall into negative water and sodium balances. Reduced food and sodium intake, together with hypodipsia, probably explain both the reduction of the extracellular compartment and the parallel decrease of weight and total body

Table 1 *Renal function on the fourth postoperative day in obstructive jaundice and sham operated groups*

	OJ group (*n* = 17)	SO group (*n* = 14)	*P*
Water balance (ml/days 1–4)	−2·4(65)	219(146)	0·0001
Bilirubin (mg/dl)	3·15(0·53)	0·19(0·15)	0·0001
Creatinine clearance (ml/min)	6·8(3·6)	10·5(4·2)	n.s
Serum osmolality (mOsm/l)	270(18)	269(8)	n s
Plasma sodium (mEq/l)	139(1)	141(3)	n s
Urine osmolality (mOsm/kg)	840(242)	945(502)	n s
Free water clearance (ml/min)	−0·10(0·04)	−0·16(0·09)	n s
Osmolal clearance (ml/min)	0·14(0·05)	0·20(0·09)	n s
Sodium excretion (mEq/24h)	1·9(1·5)	4·7(2·8)	0·0001
Sodium intake (mEq/24h)	0·73(0·27)	7·15(1·75)	0·0001
FE sodium (%)	0·29(0·31)	0·38(0·30)	n s.

OJ, obstructive jaundice, SO, sham operated, n s., not significant Results are expressed as mean(s d.). FE, fractional excretion

Table 2 *Renal function on the tenth postoperative day in obstructive jaundice and sham operated groups*

	OJ group (*n* = 17)	SO group (*n* = 14)	*P*
Water balance (ml/days 7–10)	11(65)	379(154)	0·0001
Bilirubin (mg/dl)	5·30(2·37)	0·11(0·03)	0·0001
Creatinine clearance (ml/min)	3(1)	11(6)	0·0001
Serum osmolality (mOsm/l)	266(23)	268(17)	n s
Plasma sodium (mEq/l)	139(3)	139(5)	n s
Urine osmolality (mOsm/kg)	653(151)	1103(561)	0·004
Free water clearance (ml/min)	−0·05(0·02)	−0·16(0·10)	0·002
Osmolar clearance (ml/min)	0·09(0·04)	0·25(0·10)	0·0001
Sodium excretion (mEq/24h)	1·1(0·7)	8·0(4·4)	0·0001
Sodium intake (mEq/24h)	0·78(0·33)	15·78(4·81)	0·0001
FE sodium (%)	0·27(0·21)	0·61(0·30)	0·0012

OJ, obstructive jaundice, SO, sham operated, n.s., not significant Results are expressed as mean(s d). FE, fractional excretion

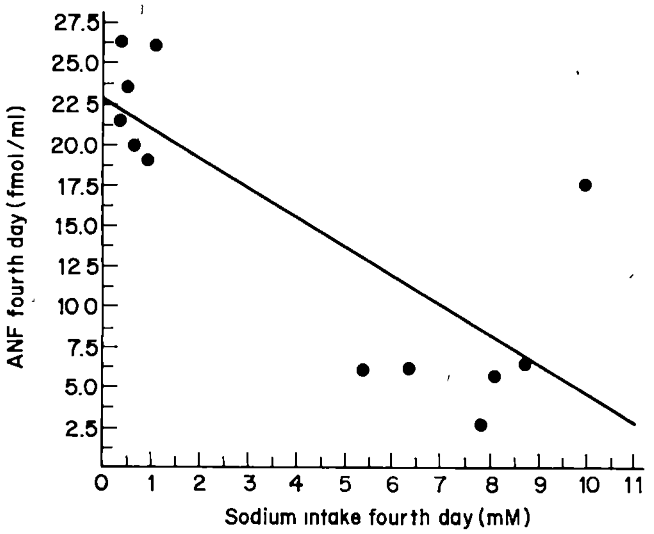

Figure 2 *Correlation between sodium intake and plasma concentration of atrial natriuretic factor in 12 rabbits on day 4 after sham operation (clustered around the right lower end of the regression line) or common bile duct ligation (clustered around the left upper end). ANF, atrial natriuretic factor.* r = −0·80, P<0·003

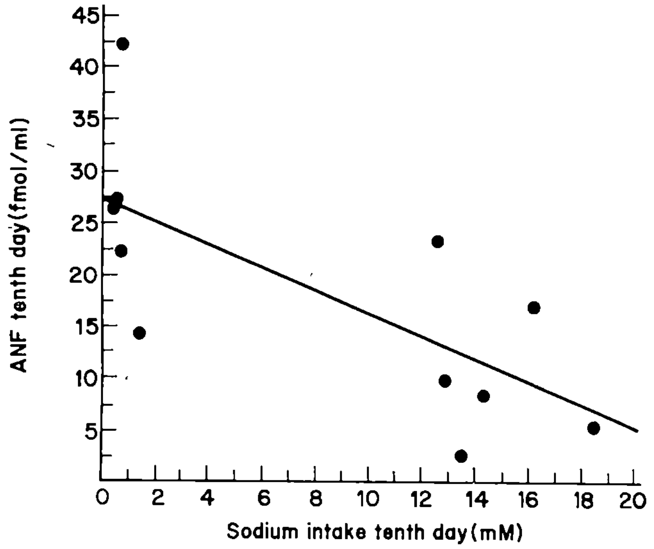

Figure 3 *Correlation between sodium intake and plasma concentration of atrial natriuretic factor in 11 rabbits on day 10 after sham operation (clustered around the right lower end of the regression line) or common bile duct ligation (clustered around the left upper end) ANF, atrial natriuretic factor* r = −0·70, P<0·02

water observed in the present model[2]. Paradoxically, in jaundiced animals the kidneys cannot respond to these restricted intakes with the expected reduction in water excretion and instead they show inappropriate diuresis associated with an impairment of ability to concentrate the urine and retain free water Yarger *et al.*[7] have also demonstrated that bile duct ligated rats show a fall in urine to plasma osmolality, but their studies were complicated by the development of ascites which makes the rat less suitable than the rabbit for this type of experiment. In the present model ascites was never demonstrated at routine post-mortem study. Ozawa *et al*[9] observed an early and significant reduction in osmolar clearance and free water reabsorption shortly after bile duct ligation in the rabbit The resulting inappropriate water and sodium loss produce a reduction in extracellular water, which in turn leads to a decreased glomerular filtration rate demonstrated by a reduction in creatinine clearance.

The mediators of the hypodipsia, loss of sodium appetite, and renal dysfunction associated with obstruction of the common bile duct are unknown In acute experiments in dogs, Levy and Finestone[6] showed that bile duct obstruction was followed in the next 4 h by an increase in urine and sodium output. This effect was partially independent of changes in the glomerular filtration rate and could be demonstrated in dogs without bile duct obstruction by means of cross perfusion studies. A humoral mediator was implicated although it could not be identified. The present results during the first 4 days of the study would support these authors' observations, since inappropriate diuresis and natriuresis with negative water and sodium balance were found during that period In addition they demonstrate that these alterations were associated with a threefold increase in plasma levels of ANF at day 4, and a twofold increase at day 10. This suggests that ANF may be an important mediator of the extracellular volume depletion found in this model of OJ, particularly during the first few days after common bile duct ligation. Ongoing studies carried out in this laboratory indicate that ANF increases as soon as 24 h after bile duct ligation.

Recent investigations suggest that elevated ANF levels might explain the major findings of our study, hypodipsia, and diuresis and natriuresis in excess of water and sodium intakes. ANF, which was found to correlate inversely with water intake during the first study period, exerts an antidypsogenic effect, probably through inhibition of the central actions of angiotensin II[10]. The diuretic and natriuretic responses to intravenously administered ANF have been well documented[11] and they have also been shown to occur after intracerebroventricular administration of ANF in dogs[12]. Impaired renal concentration could be explained by antagonism between ANF and vasopressin (ADH). In humans, intravenous ANF reduces plasma concentration of ADH[13]. In rats, ANF inhibits plasma ADH release when given either intravenously[14] or into the cerebral ventricles[10] Dense innervation of vasopressin secreting neurones by inhibiting ANF-like immunoreactive fibres has been found in the rat hypothalamus[15]. Thus the putative effects of ANF would explain most of the physiological derangements seen in the present model of common bile duct ligation.

Why ANF levels are inappropriately increased in the presence of a depleted extracellular space is not known. Perhaps release of ANF, triggered by complete biliary obstruction, may be a primary event leading to isotonic extracellular volume depletion through hypodipsia, reduced appetite for sodium, and increased renal water and sodium losses. Neurogenic pathways from the liver to organs known to contain or release ANF

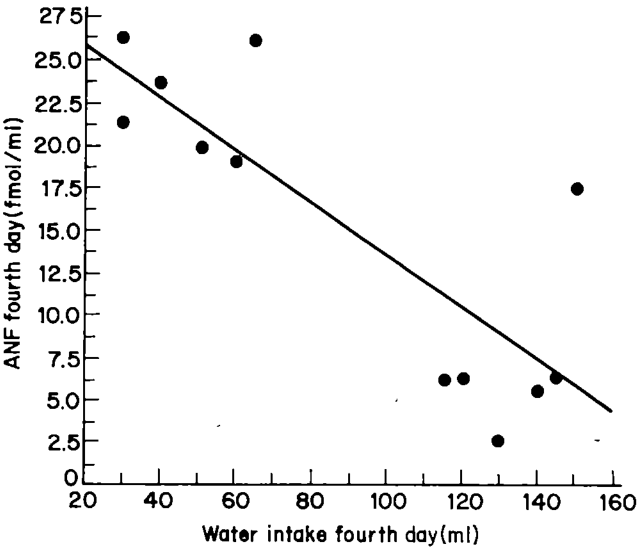

Figure 4 *Correlation between water intake and plasma concentration of atrial natriuretic factor in 12 rabbits on day 4 after sham operation (clustered around the right lower end of the regression line) or common bile duct ligation (clustered around the left upper end) ANF, atrial natriuretic factor* r = −0·80, P<0·001

(central nervous system, right atrium) may be involved but hepatic denervation did not prevent increased natriuresis after common bile duct ligation in one study in dogs[6] ANF could be present in the liver and be released to the general circulation as a consequence of an increase in biliary or portal venous pressure following bile duct ligation.

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Diagnosis of soft tissue tumours by Tru-Cut® biopsy

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Tru-Cut® biopsies were obtained from 52 consecutive patients referred with soft tissue tumours. Forty-five patients had soft tissue sarcomas; seven had benign soft tissue tumours. Of the biopsies 96 per cent provided adequate material for diagnosis. The histological diagnosis made from the Tru-Cut biopsy was compared with that made from the resected specimen. There were no false positive diagnoses of malignancy. The accuracy of Tru-Cut biopsy was 98 per cent for the diagnosis of malignancy and 94 per cent for the diagnosis of sarcoma. Tumour subtype was correctly specified in 85 per cent of sarcomas and tumour grade in 88 per cent. Tru-Cut biopsy should replace open biopsy as the primary means of diagnosis of soft tissue tumours unless a satisfactory tissue sample cannot be obtained.

Keywords: Soft tissue sarcoma, biopsy, Tru-Cut needle

Accurate histopathological diagnosis is important in the management of patients with soft tissue sarcoma[1]. It is frequently made from material obtained by open or excision biopsy, but such procedures are not wholly without complications[2,3]. Needle biopsy is less traumatic, can be performed under local anaesthesia and is less likely to compromise definitive surgery. The technique has been criticized, however, because of problems in sampling and interpretation[2].

We have previously reported a study in which Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsies were obtained from excised tumour specimens to minimize sampling errors. A correct diagnosis of soft tissue sarcoma was made in 87–98 per cent of cases[4] In this paper we report the results of a subsequent study to determine the accuracy of Tru-Cut biopsy of tumours *in situ*

Patients and methods

The study group comprised 52 consecutive patients undergoing surgery for a soft tissue tumour at the Royal Marsden Hospital. The mean age of the patients was 45 years (range 12–80 years) and 29 were male. Of the tumours 39 were situated on the limbs and limb-girdles, eight were on the trunk, one was in the parotid region and four were retroperitoneal.

A total of 34 patients were referred with clinical features of a primary soft tissue sarcoma in 11 of whom a pathological diagnosis of sarcoma had been established by open biopsy at the referring institution In the remaining 18 patients the tumour represented locally recurrent disease in 17 and metastatic disease in one.

Biopsies were obtained by percutaneous puncture after infiltration with 1 per cent lignocaine. A 14Ga Tru-Cut needle was used which provided a core of tissue whose maximum length was 20 mm Two cores were usually obtained through the same puncture wound and the biopsy was repeated if a satisfactory core, as judged by simple inspection, was not obtained. The biopsy site was chosen so that it could be excised as part of the definitive procedure and, by examining relevant computed tomography scans, neurovascular structures and areas of cyst formation were avoided. In four patients with retroperitoneal tumours, biopsy was guided by computer assisted tomography or ultrasound

Biopsy cores were placed in formalin and prepared for histological examination The slides were subsequently reviewed by one observer (C.F.), without knowledge of the clinical details, who was asked· (1) to categorize biopsies as malignant, benign, or inadequate for diagnosis; (2) to make a specific diagnosis where possible; and (3) to provide a histological grade for malignant tissue. The diagnosis was compared with the definitive report obtained by histological examination of the resected tumour. Immunohistochemical studies were undertaken on surgical specimens and occasionally on Tru-Cut samples.

Results

The final histological diagnosis of excised specimens is shown in *Table 1*. There were 45 malignant tumours and seven benign lesions. Malignant fibrous histiocytoma (MFH) accounted for 33 per cent of sarcomas.

In 42 cases Tru-Cut biopsy was reported to show a malignant tumour and this was confirmed by definitive section in each case. Eight biopsies were reported as benign and this was confirmed by definitive histology in seven cases (i.e. there was one false negative diagnosis for malignancy). Two biopsy cores were considered inadequate for diagnosis.

Of the 42 biopsies identified as malignant, 40 were specified as sarcoma and this was confirmed in each case. Two biopsies, though correctly diagnosed as malignant, were not identified as sarcoma and both were therefore counted as false negative diagnoses for sarcoma. Including the single false negative diagnosis for malignancy, there was a total of three false negative diagnoses for sarcoma.

Excluding the two inadequate biopsies the predictive value of a positive Tru-Cut diagnosis for malignancy was 100 per cent, the sensitivity 98 per cent and the overall accuracy 98 per cent. For the diagnosis of sarcoma the predictive value of a positive diagnosis was 100 per cent, the sensitivity 93 per cent and the overall accuracy 94 per cent.

Tumour subtype and grade

Among 40 biopsies correctly diagnosed as sarcoma the tumour subtype was correctly specified in 34 (85 per cent), incorrectly specified in three (8 per cent) and impossible to specify in three

Table 1 *Definitive diagnosis of 52 soft tissue tumours*

Malignant	No.	Non-malignant	No.
Malignant fibrous histiocytoma	15	Fibromatosis	5
Liposarcoma	8	Lipoma	2
Malignant schwannoma	6		
Synovial sarcoma	6		
Pleomorphic sarcoma	3		
Leiomyosarcoma	3		
Rhabdomyosarcoma	1		
Triton tumour	1		
Chondrosarcoma	1		
Indeterminate	1		
Total	45		7

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(8 per cent). Tumour grade was correctly specified in 35 biopsies (88 per cent), incorrectly specified in two (5 per cent) and impossible to specify in three (8 per cent). In the six cases in which tumour subtype was indeterminate or incorrectly specified, the grade was also indeterminate in one but correctly specified in five.

The diagnosis of the seven benign lesions was correct in each case.

Sources of error

There was one false negative diagnosis of malignancy where the biopsy was interpreted as a benign lipoma. Definitive section revealed a lipoma-like (well differentiated) liposarcoma. In two cases a diagnosis of malignancy was made but categorization was impossible. One was an extensively necrotic, poorly differentiated myxoid liposarcoma; the other was a focally necrotic MFH.

In three cases correctly identified as sarcoma the subtype was wrongly specified. Two were cases of pleomorphic MFH, which were incorrectly specified as liposarcoma and malignant peripheral nerve sheath tumour. One case was a pleomorphic leiomyosarcoma, which was incorrectly specified as a pleomorphic MFH. In three cases identified as sarcoma the subtype could not be specified; two were cases of pleomorphic MFH and one was an extensively necrotic malignant Triton tumour.

Tumour grade was incorrectly specified in two peripheral nerve sheath tumours and impossible to specify in three necrotic tumours

Complications

There were no complications from Tru-Cut biopsy among patients with soft tissue tumours of the limbs. One patient with a retroperitoneal tumour developed signs of intra-abdominal bleeding following Tru-Cut biopsy and required blood transfusion.

Discussion

Biopsy is a prerequisite in the management of patients with soft tissue tumours. A confident distinction between benign and malignant lesions cannot always be made by physical examination alone and the biological behaviour of malignant soft tissue tumours is closely related to the histological grade and tumour subtype[1].

Open biopsy requires general anaesthesia and surgical complications are reported to occur in up to 20 per cent of cases[3]. In contrast, closed biopsy is simple to perform under local anaesthesia and wound complications are exceptional – one complication in the present study in a patient with a retroperitoneal tumour.

Closed biopsy can be carried out with a Tru-Cut needle or by fine needle aspiration. We have previously evaluated both techniques using the excised specimen to minimize sampling errors[4,5]. Tru-Cut biopsy proved to be more accurate in these circumstances.

In patients with suspected soft tissue sarcoma, biopsy, whether open or closed, must be planned carefully. To avoid tumour implantation the biopsy site should be excised *en bloc* with the primary lesion[2]. This may not be easy after open biopsy, particularly if the incision has been poorly orientated[2]. After Tru-Cut biopsy the wound can be readily incorporated in the definitive resection and the risk of needle-track implantation is thereby eliminated.

Needle biopsy has been criticized principally because the quantity of biopsy material may be insufficient for accurate diagnosis[2]. In the present study, however, only 4 per cent of biopsies were considered to be inadequate. Unsuitable samples were kept to a minimum by repeating the biopsy if the sample appeared unsatisfactory on simple inspection and by examining relevant computed tomography scans before selecting the biopsy site so that cystic areas could be avoided. In most cases two biopsy cores were obtained from the tumour.

The overall accuracy for diagnosis of malignancy was 98 per cent and a diagnosis of sarcoma was specified with an accuracy of 94 per cent. Tru-Cut biopsies were examined by a pathologist (C.F.) with considerable experience in the diagnosis of soft tissue tumours and this undoubtedly contributed to the level of accuracy achieved. This study and its predecessor[4] demonstrate that a reliable diagnosis of soft tissue sarcoma can be made from the relatively small quantity of tissue obtained by Tru-Cut biopsy. If histological interpretation proves difficult, slides can be sent for review by a pathologist with a specific interest in soft tissue tumours.

Paradoxically, Tru-Cut biopsy may provide a more representative tissue sample than open biopsy. At open biopsy, unless a trocar is used[6], tissue is often taken from the surface of the tumour which typically consists of a well developed pseudocapsule. With a Tru-Cut needle tissue is obtained from within the main bulk of tumour and this may explain why the accuracy compares so favourably with that of open biopsy[3].

The only false negative diagnosis of malignancy was made in a patient with a low grade (lipoma-like) liposarcoma. This tumour can be almost indistinguishable from a benign lipoma even when the entire specimen is available for formal examination[7].

There were no false positive diagnoses of malignancy. As a result of referral practices, however, there was a total of only seven benign lesions. The specificity of Tru-Cut biopsy cannot therefore be assured. This is important because amputation is occasionally necessary to treat malignant soft tissue tumours of the extremities and a false positive diagnosis could therefore have disastrous consequences. In practice, amputation is seldom undertaken in our unit except as a salvage procedure after failed conservative surgery[8] and a definitive diagnosis is already established. If amputation is contemplated as a primary procedure and the result of Tru-Cut biopsy is in any way equivocal, there should be no hesitation in resorting to open biopsy, preferably using the technique of punch biopsy described elsewhere[6].

Histological subtype was correctly specified in 85 per cent of biopsies identified as sarcoma. An extremely pleomorphic appearance or extensive necrosis were the main reasons for inaccurate classification. Tumour grade was correctly specified in 88 per cent of biopsies identified as sarcoma and in all but one of those in which the subtype was indeterminate or incorrectly specified. Both incorrectly graded biopsies were from peripheral nerve sheath tumours whose behaviour does not necessarily correspond to the degree of differentiation[9].

Tru-Cut is as accurate as conventional open biopsy for the diagnosis of soft tissue sarcoma. Since it is simpler to perform, less expensive, almost free from complications and unlikely to compromise subsequent management we recommend that it should be used in place of open biopsy. At the Royal Marsden Hospital it is now our practice to encourage clinicians seeking advice on the management of suspected soft tissue tumours to perform a Tru-Cut biopsy and send slides of the material obtained to our pathologist for review.

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Case report

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Massive haemorrhage following endoscopic transgastric drainage of pancreatic pseudocyst

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Pancreatic pseudocysts occur in up to 15 per cent of patients following acute pancreatitis[1]. While spontaneous resolution occurs in the minority of cases after 4–6 weeks[2], the conventional surgical management of established cysts is operative drainage through the posterior gastric wall. The introduction of sensitive diagnostic techniques such as ultrasound, endoscopic retrograde cholangiopancreatography (ERCP) and computed tomographic scanning, have facilitated the development of percutaneous cyst drainage[3,4]. Recent reports document the drainage of pseudocysts using an endoscope[5,6]. Endoscopic electrocautery can be used to cut into a pseudocyst as it bulges into the gastric lumen[5]. A straight catheter can be placed through the wall to achieve limited internal drainage. Bleeding has been a theoretical risk. We report a case of endoscopic drainage of a pseudocyst which resulted in immediate, massive, life-threatening haemorrhage.

Case report

A 50-year-old Asian woman was admitted as an emergency with a 24-h history of severe upper abdominal pain. She was known to suffer from end stage renal failure for which she had successfully undergone renal transplantation 16 months earlier. Up to the time of her admission renal function was excellent with a creatinine level of 80 mmol/l while on maintenance immunosuppressive therapy of 4 mg/kg of cyclosporin and 5 mg/day of prednisolone. She had a history of intermittent flatulent dyspepsia and right upper quadrant pain On examination she was distressed but apyrexial, and had tenderness and guarding in the epigastrium She had leucocytosis and amylasaemia of 16 241 units per litre, consistent with acute pancreatitis Upper abdominal ultrasound demonstrated a distended gallbladder containing multiple small stones The pancreas was diffusely swollen and the biliary tree was normal, as were her liver function tests. Computed tomographic scanning showed changes consistent with necrosis in the midbody of the pancreas with no evidence of fluid collection. She was treated conservatively with nasogastric suction, total parenteral nutrition and antibiotics. Her condition deteriorated, she became pyrexial, hypoxic and required observation in the intensive therapy unit After 1 week her condition gradually improved but she was noted to have an epigastric mass Computed tomograpic scanning showed an oedematous pancreas with evidence of an inflammatory collection over the midbody, which was confirmed as a pseudocyst on aspiration cytology. As her condition stabilized supportive therapy was continued. Two weeks later repeat ultrasound and computed tomographic scanning showed a very large pancreatic pseudocyst (*Figure 1*) compressing the posterior wall of the stomach. As she was intermittently pyrexial with an unresolved pseudocyst after 5 weeks of observation, it was felt that an attempt at endoscopic cyst drainage was appropriate to avoid surgical intervention in an immunocompromised patient An ERCP, performed by an experienced gastroenterologist, demonstrated a patent pancreatic duct which was 3 mm wide but narrowed in the body and freely communicating with the pancreatic pseudocyst (*Figure 2*). It was not considered possible to drain this by a stent across the papilla With the patient sedated and using an end-viewing fibreoptic endoscope, the stomach was visualized and a large bulge identified on the lesser curve At the apex of the bulge a cautery needle was used to penetrate the mucosa and a jet of turbid fluid was released from the cyst The heated wire was replaced with a 'sphincterotomy' wire which was used to enlarge the puncture site to 1 cm to improve the cyst drainage This manoeuvre was followed by brisk arterial haemorrhage from the cyst wall. The patient developed tachycardia and was immediately transferred to theatre where laparotomy showed 2 l of blood in the stomach She required a total of 8 units of blood transfusion The right gastric artery was bleeding briskly in the edge of the thickened cyst wall. The vessel was oversewn and haemostasis achieved The cyst cavity which extended around the renal vessels inferiorly was empty and was irrigated. The cystgastrostomy was enlarged and the free edges oversewn for haemostasis The gallbladder, which contained multiple stones, was also removed. Following surgery she made an uneventful recovery and 3 months later is well with normal renal function, no evidence of pancreatic exocrine or endocrine insufficiency and no evidence on ultrasound of recurrent pseudocyst formation.

Discussion

While minimally invasive procedures are becoming attractive options, particularly when dealing with high risk patients, they

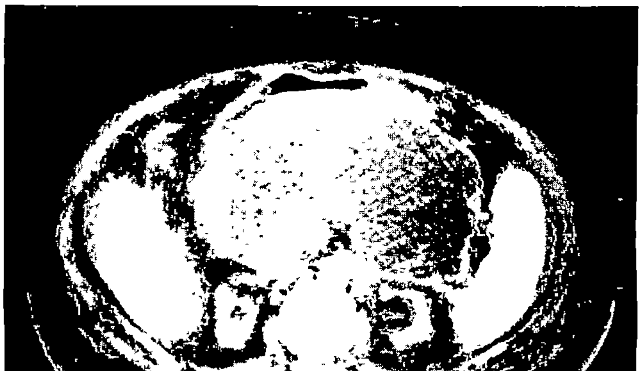

Figure 1 *A very large pseudocyst shown on computed tomographic scanning to have replaced most of the pancreas*

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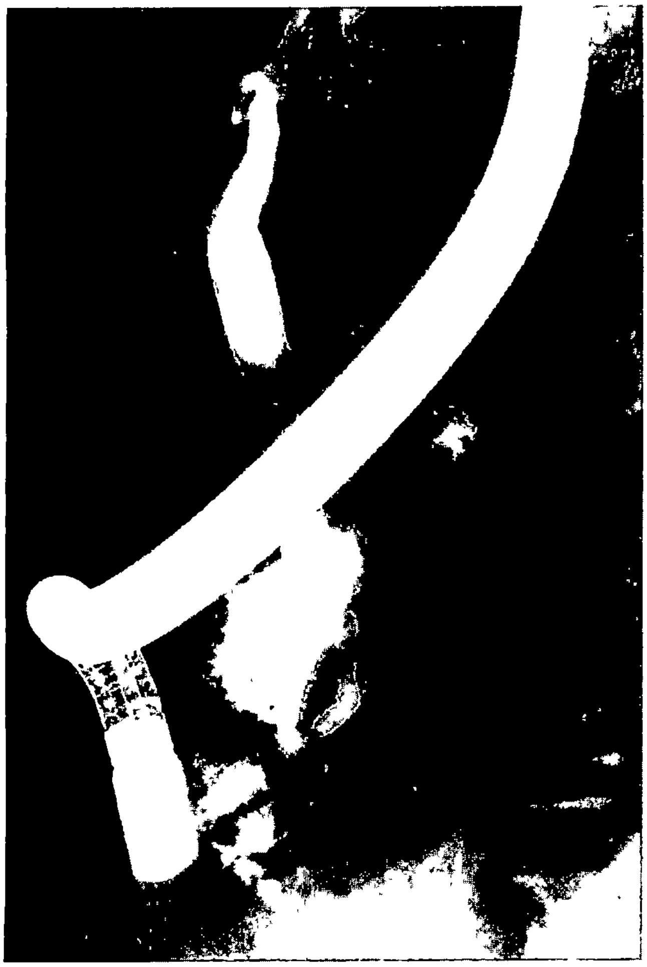

Figure 2 *Endoscopic retrograde cholangiopancreatography shows a displaced, compressed, pancreatic duct communicating with the pseudocyst*

none the less carry a significant morbidity rate. In a previous case report of endoscopic transgastric drainage of a pancreatic pseudocyst, the cyst decreased in size without bleeding, although the patient died from septicaemia[5]. Two cases of bleeding, one of which resulted in death, occurred in a series of 19 patients treated by endoscopic transduodenal drainage of cysts associated with chronic calcifying pancreatitis[6]. As illustrated by this case, careful preparation and adequate surgical support are essential if the potential benefits of this new approach to the management of pancreatic pseudocysts are to be realized.

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Complications and local recurrence following lymphadenectomy

We have retrospectively reviewed the case notes of 208 patients undergoing either cervical, axillary, or inguinal lymphadenectomy with a view to determining the factors that predispose to complications and local recurrence. The most frequent complications were wound infection, seroma formation, paraesthesiae and lymphoedema. The main predisposing factor for complications was anatomical site; wound complications occur with twice the frequency in the inguinal lymphadenectomy group than in the two other sites. Preresection biopsy was also associated with an almost twofold increase in complications, while fine needle aspiration cytology was not. The two major factors influencing the incidence of local recurrence were the stage of the disease process and the use of preresection biopsy. There was a steady increase in the incidence of local recurrence with increasing stage of regional disease. In addition, local recurrence was almost twice as common in patients who had undergone biopsy before resection when compared with patients who either did not have tissue sampling before resection or had fine needle aspiration cytology alone. We conclude that fine needle aspiration cytology is safe and the investigation of choice in patients undergoing lymphadenectomy. In contrast, preresection biopsy should be avoided as it promotes both complications and local recurrence. In addition, wound complications and lymphoedema are frequent following lymphadenectomy, especially following inguinal dissection.

Keywords: Lymphadenectomy, melanoma, squamous cell cancer, head and neck, thyroid, parotid, surgery

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Lymphadenectomy in any site is generally performed either as a therapeutic resection of clinically involved nodes or as a prophylactic or staging procedure in patients without palpable nodes[1–3]. Most patients with clinically overt regional disease should undergo resection as failure to do so is frequently associated with problems that should be avoided, such as fungation and secondary infection[1–4].

Indications for prophylactic lymphadenectomy are less clear. Two studies show differing opinions: firstly that prophylactic lymphadenectomy does not convey a survival advantage in patients with melanoma[5,6], and secondly, retrospective data indicate a survival advantage following prophylactic lymphadenectomy for melanomas of 'medium thickness' (1·5–4·0 mm in thickness)[2,7].

Lymphadenectomy in the absence of overt regional disease is performed in selected patients for staging of disease[3,8–11] In the patient with tongue carcinoma ($> T_1$ lesion) occult regional disease is present in approximately 30 per cent[3,8,11], and supraomohyoid lymphadenectomy is often performed to avoid 'understaging' and undertreating the disease[8,11].

Many factors concerning node dissection are far from clear; in particular the following require clarification:

1. How frequent and how serious are complications?
2. What factors predispose to complications?
3. Is it safe to biopsy or fine needle aspirate regional disease?
4. What factors predispose to complications and/or local failure?
5. Does the use of adjuvant radiation minimize local recurrence?

We have therefore reviewed our local experience of 208 patients undergoing lymphadenectomy.

Patients and methods

Case notes of the 208 patients were reviewed

Histological diagnosis and stage of regional disease

In the neck. N_1 was one group of nodes of <3 cm in diameter; N_2 was two groups of nodes of 3–6 cm in diameter, and N_3 was bilateral nodes or nodes >6 cm in diameter[11]

In the axilla N_1 was disease at level one (inferior to pectoralis minor tendon) N_2 and N_3 were disease deep to and above pectoralis minor tendon respectively[12]

In the groin. N_{1-3} was disease measuring <3 cm, 3–6 cm and >6 cm respectively.

Type of operative procedure employed

In the neck the procedures included limited (supraomohyoid or posterior triangle), radical or modified neck dissection. The axillary dissections were either full axillary clearance (levels 1–3) or limited resections (levels 1 and 2), and the groin dissections were either superficial (inguinal) or combined superficial and deep (iliac) dissections

Local recurrence and complications

Complications were documented as early (in hospital) or late (persisting >1 month after discharge) Local recurrence was defined as disease re-occurring in a previously resected site.

Preoperative tissue sampling

For patients who were first assessed by the senior author, node biopsy was only performed under exceptional circumstances, and the diagnosis of regional disease was made on the basis of histology of the primary

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Table 1 *Histology of primary lesion* versus *site of lymphadenectomy*

	Neck	Axilla	Groin
Melanoma	15	34	52
Squamous cell carcinoma	47	8	3
Thyroid carcinoma	16	–	–
Salivary carcinoma	9	–	–
Other	12	9	3
Total	99	51	58

Table 2 *Stage of disease* versus *site*

	Neck	Axilla	Groin	Total
N_0	22	10	10	42
N_1	39	23	28	90
N_2	20	13	16	49
N_3	18	5	4	27
Total	99	51	58	208

Table 3 *Incidence of preoperative tissue sampling*

	Neck	Axilla	Groin	Total
Biopsy	26	8	12	46
Fine needle aspiration cytology	18	4	2	24
Both	3	1	–	4
Total	47	13	14	74

Table 4 *Incidence of complications* versus *site*

	Neck	Axilla	Groin	Total
Immediate	53/99 (53)	26/51 (51)	52/58 (90)	131/208 (63·0)
Long term	24/99 (24)	10/51 (20)	28/58 (48)	64/208 (29·8)

Values in parentheses are percentages

lesion coupled with clinical examination, either alone or in conjunction with fine needle aspiration (FNA) cytology.

Technique of lymphadenectomy

The nodal dissections were performed using standard techniques as outlined by others[3,4,7,13–15] In general terms this usually involved mobilization of generous skin flaps, and resection of the regional bed as a monobloc with preservation of the associated vascular and neurological structures. (Radical neck dissection involved sacrificing the internal jugular vein while in all other lymphadenectomies the vein was preserved.)

Results

Primary pathology

In 50 per cent of cases melanoma was the primary lesion, accounting for 15 per cent of cervical dissections, 67 per cent of axillary dissections and 89 per cent of groin dissections. In the neck, the most common primary was squamous cell carcinoma accounting for 52 per cent (*Table 1*).

Stage of disease versus *site*

Stage of disease, stratified for site, is shown in *Table 2*.

Extent of lymphadenectomy

Of 99 cervical procedures 68 were radical dissections, 13 were modified, ten were supraomohyoid only, four were posterior triangle only, and four were part of a composite procedure.

Of 51 axillary procedures 35 were full dissections, the remainder being partial. Forty-nine groin dissections were superficial, the remainder being combined superficial and deep.

Preoperative tissue sampling

Forty-six patients underwent preoperative biopsy and 24 patients had FNA (*Table 3*).

Age of patients and hospital stay

The mean patient age was 57 years (range 16–89 years). The mean stay in hospital was 12 days, the values being 8, 12 and 15 days for dissections of axilla, neck and groin respectively.

Complications

Complications overall. Seventy per cent of patients experienced immediate complications, and 31 per cent had long term complications. Complications were more common following groin surgery than in the other sites (*Tables 4* and *5*)

Complications as a function of stage of disease Complication rate was independent of disease stage (*Table 6*).

Influence of radiation on complications. Preoperative radiation was administered to 11 of the 99 patients in the neck dissection group, and to four of the 58 patients in the groin dissection group.

There was no obvious effect of prior irradiation on the incidence of early complications, but lymphoedema was more common in the irradiated group (*Table 7*).

Table 5 *Complications following lymphadenectomy*

	Neck	Axilla	Groin	Total
Immediate				
Seroma	10	6	12	28
Wound infection	9	6	25	40
Wound breakdown	4	1	10	15
Lymphoedema	5	1	19	25
Lymphorrhoea	3	3	13	19
Paraesthesia	18	1	1	20
Long term				
Lymphoedema	4	4	23	31
Paraesthesia	14	–	–	14
Hernia	–	–	3	3

Table 6 *Complications* versus *stage of regional disease*

	Neck	Axilla	Groin	Total
Immediate				
N_0	12/22	3/10	8/10	25/42 (55)
N_1	25/39	13/23	26/28	64/90 (71)
N_2	8/20	6/13	14/16	28/49 (57)
N_3	8/18	4/5	4/4	16/27 (59)
Long term				
N_0	7/22	2/10	6/10	15/42 (36)
N_2	6/39	3/23	15/28	24/90 (27)
N_2	8/20	3/13	5/16	16/49 (33)
N_3	3/18	2/5	2/4	7/27 (26)

Values in parentheses are percentages

Table 7 *Complications* versus *preoperative radiation*

	Preoperative radiation	No radiation
Wound seroma	2/15 (13)	20/146 (13·7)
Wound infection or breakdown	3/15 (20)	25/146 (17·1)
Late lymphoedema	4/15 (27)	27/146 (18·5)

Values in parentheses are percentages

Complications as a function of preoperative biopsy. Preoperative biopsy was associated with a higher incidence of complications, while FNA was not (*Table 8*).

Complications versus *extent of surgery.* Lesser procedures were followed by a lower complication rate than the radical procedures (*Table 9*).

Local recurrence

The incidence of local recurrence was influenced by the stage of disease, whether preoperative biopsy procedures had been performed, and whether preoperative radiation had been used.

Local recurrence as a function of stage of disease Local recurrence was progressively more common with increasing stage of regional disease (*Table 10*).

Local recurrence and preoperative tissue sampling. The incidence of local recurrence was similar in the patients who had not undergone tissue sampling or had undergone FNA. In contrast, local recurrence was almost twice as high in the patients who had undergone biopsy before definitive surgery (*Table 11*).

Local recurrence versus *extent of surgery.* The extent of surgery had no effect on the incidence of local recurrence. Overall, the rates of local failure were 31 per cent and 29 per cent for the radical and less than radical groups respectively.

Local recurrence as a function of radiation. The rate of local recurrence was approximately twice as high in the patients who received radiation (*Table 12*). When the effect of radiation on local recurrence was assessed with stratification of the patients for the stage of regional disease there was no obvious advantage for the irradiated N_{2-3} patients (*Table 13*).

Local recurrence versus *histology.* The histology of the tumour had little impact on the incidence of local failure (*Table 14*).

The significance of local recurrence Local recurrence was associated with an ominous outcome. A variety of treatment modalities was employed in an attempt to manage local recurrence (including surgical excision, radiation, and/or chemotherapy); all were unsuccessful, and only three patients were alive 1 year after developing recurrence.

Table 8 *Complications* versus *preoperative biopsy*

	Biopsy	Fine needle aspiration cytology	No biopsy
Wound seroma	8/46 (17)	3/24 (13)	19/137 (13 9)
Wound infection or breakdown	15/46 (33)	3/24 (13)	20/137 (14·6)
Late lymphoedema	11/46 (24)	3/24 (13)	21/137 (15·3)

Values in parentheses are percentages

Table 9 *Complications* versus *extent of resection*

	Neck		Axilla		Groin	
	Radical	Lesser	Full	Partial	Deep	Superficial
Seroma	7/63 (11)	2/33 (6)	5/38 (13)	1/13 (8)	2/9 (22)	12/49 (24)
Infection or breakdown	5/63 (8)	2/33 (6)	6/38 (16)	0/13 (0)	2/9 (22)	22/49 (45)
Lymphoedema	3/63 (5)	1/33 (3)	4/38 (11)	0/13 (0)	7/9 (78)	19/49 (39)

Values in parentheses are percentages

Table 10 *Local recurrence* versus *stage of disease*

	Neck	Axilla	Groin	Total
N_0	7/22 (32)	1/10 (10)	1/10 (10)	9/42 (21)
N_1	9/39 (23)	4/23 (17)	7/28 (25)	20/90 (22)
N_2	5/20 (25)	5/13 (38)	7/16 (44)	17/49 (35)
N_3	7/18 (39)	3/5 (60)	3/5 (75)	13/27 (48)

Values in parentheses are percentages

Table 11 *Local recurrence* versus *preoperative biopsy*

	Neck	Axilla	Groin	Total
Biopsy	11/27 (41)	4/9 (44)	5/12 (42)	20/48 (42)
Fine needle aspiration cytology	4/18 (22)	0/1 (0)	1/5 (20)	5/24 (21)
Nil	12/54 (22)	10/41 (24)	11/42 (26)	33/137 (24 1)

Values in parentheses are percentages

Table 12 *Local recurrence* versus *radiation*

	Neck	Axilla	Groin	Total
Preoperative ERT	5/12 (42)	0 0 (0)	2/3 (67)	7/15 (47)
Postoperative ERT	13/35 (37)	3/9 (33)	5/6 (83)	21/50 (42)
No ERT	12/52 (23)	10/42 (24)	12/49 (24)	31/143 (23 8)

ERT, external beam radiation therapy Values in parentheses are percentages

Table 13 *The effect of adjuvant radiation on local recurrence*

Stage	Neck	Axilla	Groin	Overall
N_{0-1}				
No radiation	7/33	4/31	5/35	16/99 (16)
Plus radiation	10/28	1/3	3/3	14/34 (41)
N_{2-3}				
No radiation	5/19	6/11	7/14	18/44 (41)
Plus radiation	8/19	2/6	4/6	14/31 (45)

Values in parentheses are percentages

Table 14 *Histology* versus *local recurrence*

	Melanoma	Squamous cell carcinoma	Other
Axilla	10/34 (29)	2/8 (25)	1/3 (33)
Groin	14/52 (27)	1/3 (33)	1/3 (33)
Neck	28/101 (27·7)	15/47 (32)	8/33 (24)
Overall	28/101 (27 7)	18/58 (31)	10/39 (26)

Values in parentheses are percentages

Discussion

Our study indicates that complications and local recurrence are common following lymphadenectomy and that in many cases there are common predisposing factors.

Complications were common following lymphadenectomy in all sites but most were minor and not life-threatening. Approximately two-thirds of patients developed early complications, and most of these were wound problems (infection, seroma formation, etc.). Thirty per cent were left with long term complications, most commonly lymphoedema, and the most obvious predisposing factor was the anatomical site of the lymphadenectomy: immediate complications following groin dissection were twice as high as in the two other sites.

A number of factors explain the high incidence of early complications following groin dissection. First, the volume of lymph draining into the inguinal nodes is far greater than into either the axillary or cervical nodes[16], explaining the higher incidence of seromas and lymphorrhoea. Second, the blood supply to the cutaneous flaps raised as part of an inguinal dissection is not as good as in the neck (where the use of subplatysmal plane allows the skin flaps here to be myocutaneous[17]).

The incidence of wound infection overall was low. Forty patients (19·2 per cent) developed a wound infection, but only in 15 (7·2 per cent) was this associated with wound breakdown – an acceptable rate compared with the reports of others[13,18–20]. Prophylactic antibiotics were used in most patients (Cefoxitin®, Merck, Sharp and Dohme, Auckland, New Zealand, or Augmentin®, Beecham Laboratories, Auckland, New Zealand, were administered on induction, and then 6-hourly for 24 h). These broad spectrum agents provide cover for both aerobes and anaerobes. They were chosen following the findings of Johnson and colleagues[19,20], and 24 h of treatment was considered adequate based on the data of Fee *et al.*[18].

In accord with the observations of others[2,4,13] we found that the most troublesome long term complication was lymphoedema, and as with early complications this was twice as common following groin dissection. The incidence of chronic lymphoedema was almost twice as high if the deep nodes had been dissected. This high complication rate following groin dissection has been reported by a number of others[4,13].

The other common late problem was paraesthesia. As part of a classical radical neck dissection the accessory nerve is divided and this results in a limitation of shoulder function and shoulder pain[14,21–23]. Short *et al.*[24] indicate that nerve preservation avoids this complication while not compromising the 'cancer operation'. However others question the appropriateness of this on the basis that such conservatism might increase local recurrence[3,8,14] In the axilla division of the intercostobrachial nerve resulted in paraesthesia in the medial aspect of the upper arm in the majority of patients while, in the groin, sensory branches of the femoral nerve were invariably divided but paraesthesia was infrequent unless the lateral cutaneous nerve of the thigh was damaged

The clinical stage of the regional disease did not have any obvious influence on the rate of either immediate or long term complications. The incidence of early complications was not higher in the patients who had received preoperative radiation probably because surgery was performed (whenever possible) within 6 weeks of completion of irradiation, and preferably within 4 weeks. Mendenhall *et al*[25] also found that wound complications after preoperative radiation were minimized if surgery was performed within 6 weeks. The rate of long term lymphoedema was higher in the irradiated patients, probably reflecting the known effects of radiation to promote fibrosis and impair lymphatic and venous function[26].

Preoperative FNA cytology did not predispose to either early or late complications but the use of open biopsy before definitive surgery was associated with a two to threefold increase in the rate of wound infection/breakdown and a 50 per cent increase in the rate of chronic lymphoedema. In some instances the use of an inappropriate biopsy incision coupled with undercutting of skin flaps resulted in the definitive procedure being a more difficult operation than would have been the case had biopsy not been performed. The extent of resection influenced the rate of complications and chronic lymphoedema These complications were almost twice as common following groin dissection when the iliac nodes were also removed – findings which are in general agreement with others[4,13].

Two factors having a prominent effect on the risk of local recurrence were the stage of the regional disease and the use of preoperative biopsy. The extent of the surgery had no effect, suggesting that the degree of surgery performed was appropriate. Koea and Shaw[11], and others[8,15] have previously shown that the inappropriate use of conservative surgery in patients with regional disease is associated with an unacceptable rate of local recurrence. For example suprahyoid neck dissection for clinical stage N_{1-2} tongue cancer is frequently associated with local failure lower in the neck[11] and when the patients were stratified on the basis of disease stage the histology of the disease (melanoma *versus* squamous cell carcinoma) had little impact on the incidence of local recurrence.

Local recurrence increased in parallel with stage of disease[1,3,4,8–10,14,15,27] especially in the presence of bulky disease, disease at multiple levels or, in the neck, the presence of extracapsular spread[27–29].

The incidence of local recurrence in those patients who did not have biopsy before surgery was remarkably constant (24–26 per cent) and lower than in those who had undergone biopsy. This supports the concept proposed by Martin[15], and stressed more recently by Shah *et al.*[8], McComb and Fletcher[30], and Shaha *et al.*[31], that biopsy of regional disease is contraindicated unless unavoidable. Razack *et al.*[32], however, found that local recurrence in patients who had undergone biopsy before definitive surgery was not higher when compared with historical controls. Wang *et al.*[28], Parsons *et al.*[33] and McGuirt and McCabe[34] came to this conclusion when the primary treatment modality was radiation. Factors regarding choice of treatment modality may explain the difference between our results and those of others[28,33,34].

FNA is a safe and useful investigation for patients with regional disease. Shaha *et al.*[31] used FNA as a routine procedure in the evaluation of cervical lymphadenopathy and found that the diagnostic accuracy was 96 per cent, that complications were minimal, and that there was no suspicion that the procedure predisposed to local recurrence The accuracy, cost-effectiveness and safety of FNA was confirmed by Smith *et al.*[35] and Weymuller *et al.*[36]. Open biopsy should only be performed if unavoidable[28,32,33] and FNA cytology is the preferred diagnostic technique[31].

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Hyperthermic isolated perfusion with melphalan in the treatment of advanced malignant melanoma of the lower limb

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A retrospective study of 91 patients with malignant melanoma treated by lower limb isolated hyperthermic regional perfusion was performed. Objective response in patients with evaluable disease was 78 per cent. The role of perfusion as primary treatment of large melanomas of the foot is confirmed and recommended. Control of locoregional disease and limb salvage remains a valuable and attainable therapeutic goal using this technique.

Keywords: Malignant melanoma, chemotherapy, perfusion

Treatment of malignant melanoma by hyperthermic isolated regional perfusion is practised in only a few centres in the UK. We report our current indications, technique and results of isolated limb perfusion in 91 patients who were at high risk of developing further locoregional recurrent disease.

Patients and methods

A retrospective study was carried out on patients presenting with malignant melanoma who were treated by lower limb isolated perfusion between 1979 and 1987 at the Westminster and Royal Marsden Hospitals, London. Ninety-one patients are reported who were at high risk of developing locoregional recurrent disease; there were 20 men and 71 women with a mean(s.e.m.) age of 58·6(1·3) years.

The majority of patients selected had non-nodal regional recurrences that were too numerous or recurred too frequently for multiple local excisions. Patients presenting with extensive tumours of the foot, where amputation or primary excision and grafting would have severely compromised function, were also selected.

Malignant melanoma was confirmed by aspiration cytology or biopsy in all cases before perfusion. All patients were screened for evidence of disseminated disease and staged according to the M. D. Anderson Hospital Classification (*Table 1*).

Perfusion in 69 cases was via the external iliac vessels where cannulation was preceded by an ilio-obturator block dissection. In all 22 patients with disease clinically confined below the knee, perfusion was prospectively performed at the femoral level without block dissection.

The extracorporeal circuit comprised a rotary roller pump and a paediatric Venotherm® (Polystan, Ballerup, Denmark) oxygenator with integral heat exchanger. The system was primed with 500 ml homologous blood and 500 ml Hartmann's solution. Flow rates ranged from 250 to 300 ml/min for femoral and from 300 to 600 ml/min for iliac perfusion. All perfusions were hyperthermic, the arterial inflow being maintained at 40–41°C. Limb temperature was monitored by intramuscular and subcutaneous needle thermocouples inserted in the calf, thigh and foot. The leg was covered to assist maintenance of a foot temperature of 39–40°C. For iliac perfusions, isolation was achieved by applying two layers of Esmarch bandage around the upper thigh and a Steinmann's pin in the os ilium. For femoral perfusions a pneumatic tourniquet was placed around the upper thigh.

Melphalan (L-phenylalanine mustard) was administered when the perfusion conditions were stable and the foot temperature had reached 37°C. A total dose of 1·5 mg/kg for femoral and 2 mg/kg for iliac perfusions was administered in three divided doses given 10 min apart. Perfusion continued for a further 30 min after the final dose. The limb was then flushed with 1000 ml of normal saline and the vessels repaired. Throughout the procedure the circuit arterial pressure was continuously monitored and adjusted, maintaining a level just below systemic to limit leakage from the extracorporeal to the systemic circulations[1].

All patients were reviewed 6 weeks after operation and at 3-monthly intervals thereafter. Those with evaluable disease were assessed for initial response to perfusion. Complete and partial response (>50 per cent reduction in measurable disease area, sustained for at least 2 months) were considered together as objective response. Patients with clinically positive inguinal lymph nodes, confirmed by fine needle aspiration cytology, had an inguinal block dissection 6 weeks after the perfusion, provided the distal disease had responded satisfactorily. Comparison of the effectiveness of iliac *versus* femoral perfusion was analysed with respect to disease-free intervals, using Student's *t* test.

Results

Sixty-seven patients had evaluable disease at the time of perfusion. Of these 11 had primary tumours of the foot too large for adequate limb-sparing excision and 56 had multiple regional metastatic disease which was too extensive for excisional surgery. *Table 2* shows the response rates achieved according to the stage of the disease. The recurrence data are summarized in *Table 3*. All time intervals are calculated from the date of the perfusion.

Table 1 *Clinical staging of malignant melanoma (M. D. Anderson Hospital Classification)*

Stage 0	Superficial spreading melanoma
Localized primary melanoma	
Stage Ia	Primary intact
Stage Ib	Locally excised
Local disease.	
Stage II	<3 cm from primary site
Regional metastasis:	
Stage IIIa	In transit
Stage IIIb	Nodes
Stage IIIab	In transit and nodes
Systemic metastasis	
Stage IV	Systemic disease

Table 2 *Objective response (complete and partial) in unexcised melanoma following limb perfusion*

Stage	No. of patients	Responders
Ia	11	10 (90·9)
II	6	5 (83·3)
IIIa	37	27 (72·9)
IIIb	4	3 (75·0)
IIIab	9	7 (77·7)
All	67	52 (77·6)

Values in brackets are percentages

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Table 3 *Recurrent melanoma following limb perfusion*

Stage	No. of patients (*n*)	No. with regional recurrence	No. with disseminated recurrence	No. of deaths
Ia	11	5 (45·4)	4 (36·4)	1 (9·1)
II	13	3 (23·1)	6 (46·1)	5 (38·5)
IIIa	40	12 (30·0)	23 (57·5)	17 (42·5)
IIIb	15	3 (20·0)	13 (86·7)	9 (60·0)
IIIab	12	– (–)	7 (58·3)	8 (66·6)
All	91	23 (25·3)	53 (58·2)	40 (43·9)

Values in brackets are percentages

Table 4 *Complications in 91 lower limb perfusions*

	Mild	Severe
Systemic.		
Leucopenia <2000	4	2
Thrombocytopenia	2	0
Pulmonary emboli	0	2 (1 death)
Pneumonia	0	1 (death)
Regional.		
Emergency amputation	0	0
Elective amputation	0	1 (see text)
Wound infection	10	3
Oedema	13	4
Haemorrhage	1	2
Neuropathy	0	1
Arthropathy	1	1

Stage I

Of the 11 patients with extensive primary tumours of the foot (Ia), two have progressed to IIIa disease at 20 and 46 months, and a further three to IIIb at 3, 4 and 10 months respectively.

Stage II

Three of 13 patients developed regional recurrence, two progressed to IIIa at 24 and 94 months, and one patient to IIIb at 6 months.

Stage III

Twelve of the 40 patients with stage IIIa disease later developed inguinal node metastasis (IIIab) and have had inguinal block dissections. This group comprised eight of the 31 patients following iliac perfusion (25·8 per cent) recurring at a mean(s.e.m.) of 21·6(5·2) months and four of the nine patients (44·4 per cent) following femoral perfusion recurring at a mean(s.e.m.) time of 11·0(2·6) months. Three of the 15 patients (20 per cent) with IIIb disease developed non-nodal regional recurrences (IIIab), two of whom are alive and disease-free at 7 and 11 months following local excision of these recurrences.

Fifty-three patients have developed disseminated disease during the follow-up period, at a mean time of 18·8(2·1) months.

The complications of perfusion are listed in *Table 4* Most patients developed a brisk erythematous reaction in the perfused region during the immediate postoperative period, associated with mild oedema. Significant bone marrow depletion occurred in two patients with complete spontaneous recovery. There were two major pulmonary emboli, one resulting in a postoperative death at 9 days, and the other occurring at 3 months which resolved with anticoagulant therapy A second death from bronchopneumonia occurred in a 75-year-old patient 6 weeks after perfusion. The two patients who died were excluded from subsequent analysis. No limbs were lost as a complication of perfusion but one patient with an ulcerated lesion invading the tibia had no control of local disease and major amputation was performed. Oedema persisted 3 months after perfusion in four patients perfused at the iliac level and required limb compression therapy. Two patients underwent re-exploration in the early postoperative period for secondary haemorrhage from the arteriotomy site. Two patients developed an equinus deformity. Other complications were minor and transient.

Discussion

Objective response rates of 80 per cent[2] and 83 per cent[3] have been reported following hyperthermic perfusion. It has also been claimed that adjuvant perfusion may improve survival and diminish locoregional recurrence[4,5]. The objective response rate of 78 per cent in our series is comparable to previous reports. These results are superior to those obtained from normothermic perfusion, e.g. 48 per cent[6] and 30 per cent[7]. Objective response to conventional systemic chemotherapy for cutaneous and nodal disease is 18 per cent[8]. An objective response of 44 per cent[9] has been reported following high-dose intravenous melphalan with subsequent bone marrow rescue, perhaps corresponding to the increased tissue and tumour melphalan levels attainable using this technique. Even higher tumour levels are obtained by perfusion[10].

Although perfusion therapy does not prevent locoregional recurrence it may increase the disease-free interval. Compared with historical controls[5] we observed a long disease-free interval between perfusion and locoregional recurrence (*Table 5*). These findings are compatible with results published elsewhere[5,11]. The local recurrence rate after complete response was 30 per cent in stage IIIa disease and is comparable with previously reported rates of 35 per cent[11,12].

In this series, 22 patients had femoral perfusions alone and 69 iliac perfusions combined with ilio-obturator block dissections. There is a higher incidence of inguinal node recurrence with a significantly ($P<0·05$) shorter mean(s.e.m.) disease-free interval in the femoral perfusion group (37·8 per cent at 8·7(2·0) months) compared with the iliac perfusion group (25·8 per cent at 21·6(5·2) months). This observation supports the view that iliac perfusion may eradicate sub-clinical inguinal node disease[13].

The 22 patients undergoing femoral perfusion included 11 with primary melanoma of the foot. This site carries a poor prognosis with a high regional node recurrence rate[14,15]. Martijn *et al.*[16] found that with melanomas of the foot perfusion did not extend the local disease-free interval. Sugarbaker and McBride[13] perfused all foot tumours twice, initially by iliac and then by femoral routes.

In our series of 11 patients with foot tumours where primary treament was by perfusion, the initial response was sufficient in all patients to allow subsequent conservative excision and grafting. This confirms the value of perfusion as primary treatment for large melanomas of the foot. Locoregional recurrence (two IIIa and three IIIb) subsequently developed in five cases (45·4 per cent at 16·6(7·4) months).

The femoral perfusion group were not subject to

Table 5 *Delayed development of locoregional recurrence following perfusion (months)*

Stage	Non-perfused (Ghussen[5])	Perfused (Ghussen[5])	Perfused (present study)*
I	5·7	17·7	19·6(5·4)
II	3·8	16·0	31·3(16·9)
III	6·4	23·2	15·8(7·6)
		Perfused (Lejeune[11])	Perfused (present study)*
IIIa		14·9	17·8(4·3)
IIIb		8·5	8·1(2·3)

*Values are mean(s.e.m.)

ilio-obturator block dissection and contained all the patients with foot tumours. These factors may contribute towards the poorer results of the group as a whole.

Comparison of survival statistics in melanoma is particularly prone to error because of the complexities of the known prognostic variables In this series where the median follow-up time has been 55 (range 12–96) months, the 5-year survival does not approach the levels reported by some centres[4,17] where clearly different methods of patient selection are employed. Although survival figures may be difficult to compare, tumour response and locoregional disease-free interval are easier to verify. The contribution towards locoregional control and to limb salvage is a valuable and attainable therapeutic goal, even if the patient subsequently develops systemic disease.

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Effect of defunction on cytokinetics and cancer at colonic suture lines

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An intestinal suture line potentiates experimental carcinogenesis in its vicinity, probably due to adaptive hyperplasia. By contrast, a defunctioning colostomy causes distal hypoplasia, and fewer tumours develop. Male Sprague-Dawley rats (n = *160) were used to study adaptation (assessed by a stathmokinetic technique) and carcinogenesis (induced by azoxymethane) at an end-to-end anastomosis that was raised in either functioning or defunctioned left colon. Controls had no procedure and other rats had proximal colostomy alone. Defunction had a profound antitropic effect on the colon, reducing bowel length and weight and crypt cell production rate (CCPR) by 22–56 per cent. Anastomotic CCPR was increased by a factor of 2·6 over controls: mean(s.e.m.) values of 12·71(2·85)* versus *4·87(0·41) cells/crypt/h* (P < *0·01), but defunction reduced this by 76 per cent to a mean(s.e.m.) value of 3·00(0·52) cells/crypt/h below that in the intact colon. In the left colon, 39–50 per cent of tumours were sited at the anastomosis. Compared with controls there were 77 per cent fewer tumours in defunctioned colon, but they still favoured the site of anastomosis. Neoplasms at the colostomy site accounted for 74–77 per cent of all right-sided tumours. Anastomosis and defunction have powerful but contrasting effects on colonic adaptation and carcinogenesis; when combined they tend to cancel each other out.*

Keywords: Colon cancer, suture line, faecal diversion

The intestinal tract undergoes profound hypoplasia when deprived of luminal contents or isolated from the nutrient stream[1,2]. Although this hypoplastic response is most marked in the jejunum, the colon also atrophies when surgical exclusion diverts the normal flow of faeces[3–5]. Mucosal contents of protein and nucleic acids are diminished by one-third at 1 week and by one-half at 4 weeks after defunctioning colostomy[3]. Likewise, after 22 weeks the weight and length of a colonic Thiry-Vella fistula are 55–60 per cent of control values, while crypt depth is 82 per cent and crypt cell production rate is only 25 per cent of normal[4]. Similar atrophy may occur in man, although evidence is scarce[6]. By depriving the colon of bulk, low-residue diets cause mucosal hypoplasia and inhibit cell renewal[7]. By contrast, a high-residue, non-nutrient diet preserves colonic mucosal mass[8], and irrigation of a Thiry-Vella fistula with faeces prevents hypoplastic changes[5].

There is a close association between intestinal adaptation and carcinogenesis in the gastrointestinal tract[9]. It is not surprising, therefore, that animals given a blood-borne carcinogen develop fewer colonic tumours in defunctioned bowel[3–5], an effect that is reversed by re-exposure to faeces but not by secondary bile acids alone[5].

In both small and large intestine surgical anastomoses provide a powerful local stimulus to experimental carcinogenesis[10–14]. Peri-anastomotic hyperplasia can be detected for at least the first 12 weeks of healing[12,15]. Such a mechanism could explain some suture line 'recurrences' after colorectal resection for carcinoma in man[16]. Experimental tumours also favour colostomy sites presumably because of chronic irritation[5,17].

We now examine the contrasting effects of faecal diversion and surgical anastomosis on the colon in rats exposed to azoxymethane, using a stathmokinetic technique to assess cytokinetic changes.

Materials and methods

Animals and operations

One hundred and sixty young male Sprague-Dawley rats with a mean(s.e.m.) weight of 189·4(12·7) g were allocated to either an adaptation experiment ($n = 60$) or a carcinogenesis experiment ($n = 100$) (*Figure 1*). Rats used for carcinogenesis received six subcutaneous injections of the selective intestinal carcinogen azoxymethane (Ash Stevens Inc., Detroit, Michigan, USA) at a dose of 15 mg/kg/week. Rats used for adaptation received no injections.

One week after the last injection, animals (now weighing 323(40) g) in each experiment were allocated to one of four groups (*Figure 1*). Group A acted as controls ($n = 15$ (adaptation) and 22 (carcinogenesis)) and had no operation. All other rats underwent laparotomy under light ether anaesthesia. In Group B ($n = 15$, 25) the lower descending colon was transected and intestinal continuity was immediately restored by end-to-end anastomosis with a continuous 6/0 silk suture (*Figure 2a*). Group C ($n = 15$, 25) had an end colostomy raised in the mid-transverse colon (*Figure 2b*). The proximal end of the defunctioned bowel was closed with a 4/0 silk suture and returned to the abdomen, while the colostomy was sutured to the abdominal skin in the left hypochondrium with interrupted 6/0 chromic catgut sutures. Animals in group D ($n = 15$, 28) had both colostomy in mid-transverse colon and transection re-anastomosis in the lower descending colon (*Figure 2c*), their colonic suture lines were thus created within defunctioned bowel.

All animals were given vitamin K_1 0·25 mg/kg at the end of each operation to prevent postoperative bleeding previously found to be troublesome in this strain of rat[18]. Ten rats died in the early postoperative period from intestinal obstruction ($n = 6$) or pneumonia ($n = 4$), and another rat died 2 weeks later from intestinal obstruction.

Intestinal adaptation

During the 14th week of the study all rats in the adaptation group ($n = 56$) were weighed and then killed at intervals 40–180 min after intraperitoneal (i.p.) administration of the stathmokinetic agent vincristine sulphate (Oncovin®, Eli Lilly, Basingstoke, UK). To bring about metaphase arrest within the intestinal crypts and to minimize

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diurnal fluctuations in cell proliferation rates[19,20], vincristine 1 mg/kg i.p was given at 09 00 hours on four successive days to all rats within one group The colon and rectum distal to the colostomy (groups C and D) or distal to the mid-transverse colon (groups A and B) were excised, stripped of mesentery and fat, opened, cleaned with normal saline and then gently dried. After weighing, each piece of left colon was suspended against a vertical scale with a standard weight (4·0 g) for measurement of length.

To determine crypt cell production rate (CCPR) in the right and left colon, small segments of bowel were excised from the ascending colon halfway between the caecum and mid-transverse colon (or colostomy), and from the lower descending colon In groups B and D the area of previous transection was identified; the anastomosis was excised together with the bowel for 3 mm on either side. In groups A and C a similar segment of bowel was excised at the corresponding site Samples were fixed in Carnoy's fluid for 4 h and were stored in 70 per cent ethyl alcohol After staining by the Feulgen reaction for DNA[19], the mucosa was stripped off the muscle coat and individual crypts were separated by microdissection[21]. The mean number of metaphase figures in 15–20 crypts was plotted against time after vincristine administration. CCPR was calculated by measuring the slope of the regression line[19].

Tumour yields

Rats in the carcinogenesis experiment were killed 26 weeks after the initial dose of azoxymethane ($n = 84$) or earlier if distressed or moribund ($n = 6$). The entire colon and rectum was removed, opened, washed with normal saline and examined for evidence of neoplasia Tumours or suspected tumours were excised and fixed in 10 per cent formalin Later, 5 μm sections were prepared and stained with haematoxylin and eosin for histological examination. In rats that had undergone intestinal transection there was no difficulty in identifying the site of the anastomosis either as a clear-cut raised area or by the presence of suture material. Any tumours arising within 3 mm of an anastomosis or within 5 mm of a colostomy site were considered separately

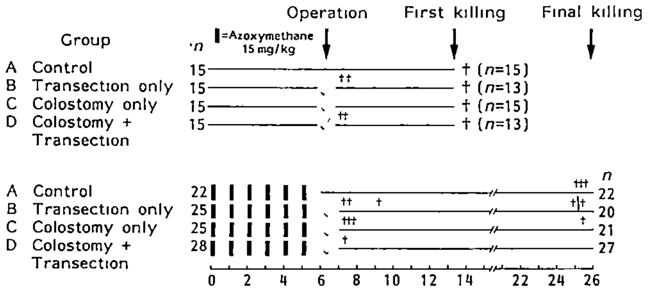

Figure 1 *Experimental design· † rat dying prematurely*

Statistical analysis

Regression lines were compared by Student's *t* test Body-weight and tumour yields were analysed by the Kruskal–Wallis test and subsequently compared by the Mann–Whitney *U* test

Results

In addition to the early postoperative deaths, six rats died or were humanely killed between 24 and 26 weeks (*Figure 1*). The causes of death were obstructing colonic tumours ($n = 3$), ear canal tumours ($n = 2$) and metastatic colonic cancer ($n = 1$). These six animals were included in the overall analysis of tumour yield ($n = 90$).

Body-weights (Table 1)

Animals with colostomy (groups C and D) weighed 10–13 per cent less at the time of death than those with intact colons (groups A and B), but these differences were not significant.

Bowel length and weight (Table 2)

Compared with controls (group A), the length of the defunctioned left colon (groups C and D) was 22–24 per cent less and its weight was 39–42 per cent less. Transection alone (group B) had no effect.

Table 1 *Body-weights at killing*

Group		Body-weight (g)
Adaptation:		
A	Control	385(41)
B	Transection only	387(37)
C	Colostomy only	350(22)
D	Colostomy + transection	340(35)
Carcinogenesis		
A	Control	550(31)
B	Transection only	541(47)
C	Colostomy only	499(42)
D	Colostomy + transection	489(34)

Data are mean(s.e m.)

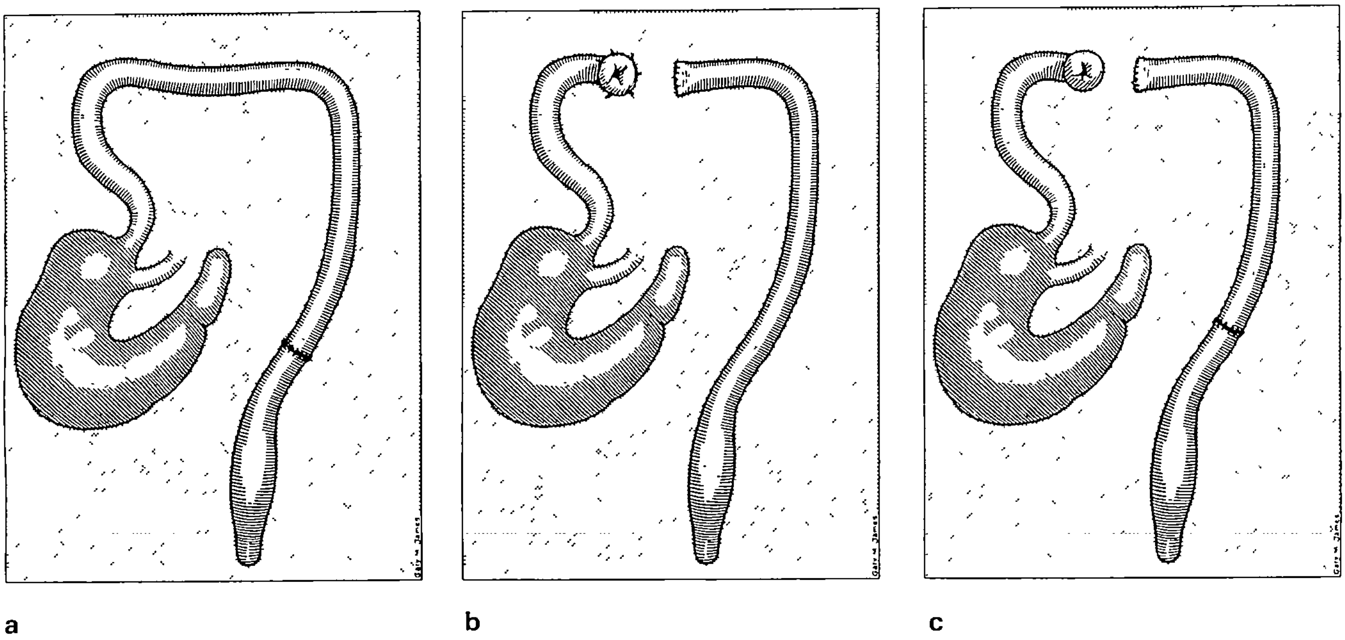

Figure 2 *Operations performed* **a** *transection of the descending colon,* **b** *colostomy alone,* **c** *colostomy plus transection of the descending colon*

Crypt cell production rate (Table 3)

CCPR in the right colon was determined for rats with colostomies (groups C and D) and those without stomas (groups A and B). The presence of a colostomy increased CCPR in the ascending colon by 35 per cent. In the left colon the most striking finding was the high CCPR at the site of anastomosis in functioning colon (161 per cent of controls). CCPR at the defunctioned anastomosis (group D) was 40 per cent higher than the defunctioned left colon of group C and 38 per cent lower than controls, but these differences were not significant. Defunction alone lowered CCPR by 56 per cent, and CCPR at the defunctioned anastomosis (group D) was 76 per cent lower than at the functioning anastomosis (group B).

Tumour yields (Figure 3)

In functioning colon, suture lines and colostomy sites produced very high yields of neoplasms. Indeed, suture line tumours accounted for almost half the left-sided lesions in group B, and in the right colon (groups C and D) colostomy tumours made up 74–77 per cent of the total number. In the right colon (*Figure 3b*), animals with colostomy alone (group C) had 33 per cent fewer (non-stomal) tumours than controls, but there was no difference in tumour yields between groups B and D. Excluding the anastomotic sites, colonic defunction lowered tumour yields in the left colon by 73–79 per cent (*Figure 3a*). Defunction also reduced anastomotic tumours by 83 per cent. Of 33 tumours found in the left colon of 27 rats with a defunctioned anastomosis (group D), 13 (39 per cent) were at the suture line and five (15 per cent) were found where the blind colonic end had been oversewn. Thus even a defunctioned suture line was a preferential site for the development of tumours.

Discussion

In line with previous studies[3–5] we have demonstrated that defunctioned colon is hypoplastic, has a lower CCPR and is more resistant to neoplasia than intact colorectal mucosa. In these respects defunctioned colon behaves in a very similar fashion to small bowel excluded from the luminal stream[2,9]. Whereas isolated small bowel can mount a hyperplastic response to jejunal resection[22], humoral stimuli such as enteroglucagon are much less effective in the colon[4]. Unlike partial enterectomy, therefore, partial colectomy has little bearing on tumour yields in the remaining large bowel[13].

Our data confirm that colostomy sites and surgical anastomoses are favoured areas for experimental carcinogenesis[9,13]. Ordinarily very rare in rodents, 'spontaneous' intestinal cancers have been reported at each site[13,17]. For anastomotic tumours to develop, at least one bowel end must

Table 2 *Length and weight of left colon in adaptation experiment*

Group		Length (cm)	Weight (g)
A	Control	14·5(0·6)	1·27(0·10)
B	Transection only	15·4(0·9)	1·25(0·13)
C	Colostomy only	11·4(1·0)*	0·78(0·07)*
D	Colostomy + transection	11·0(0·9)*	0·74(0·10)*

Data are mean(s.e.m.), * $P<0·001$ *versus* control

Table 3 *Crypt cell production rates (CCPR)*

Site	CCPR (cells/crypt/h)
Right colon	
No colostomy (A and B)	10·04(1·13)
Distal colostomy (C and D)	13·57(1·26)*
Left colon	
Control (A)	4·87(0·41)
Transection (B)	12·71(2·85)†
Defunction (C)	2·14(0·20)†
Defunction + transection (D)	3·00(0·52)‡

Data are mean(s.e.m.), * $P<0·05$; † $P<0·01$ *versus* control; ‡ $P<0·01$ *versus* transection

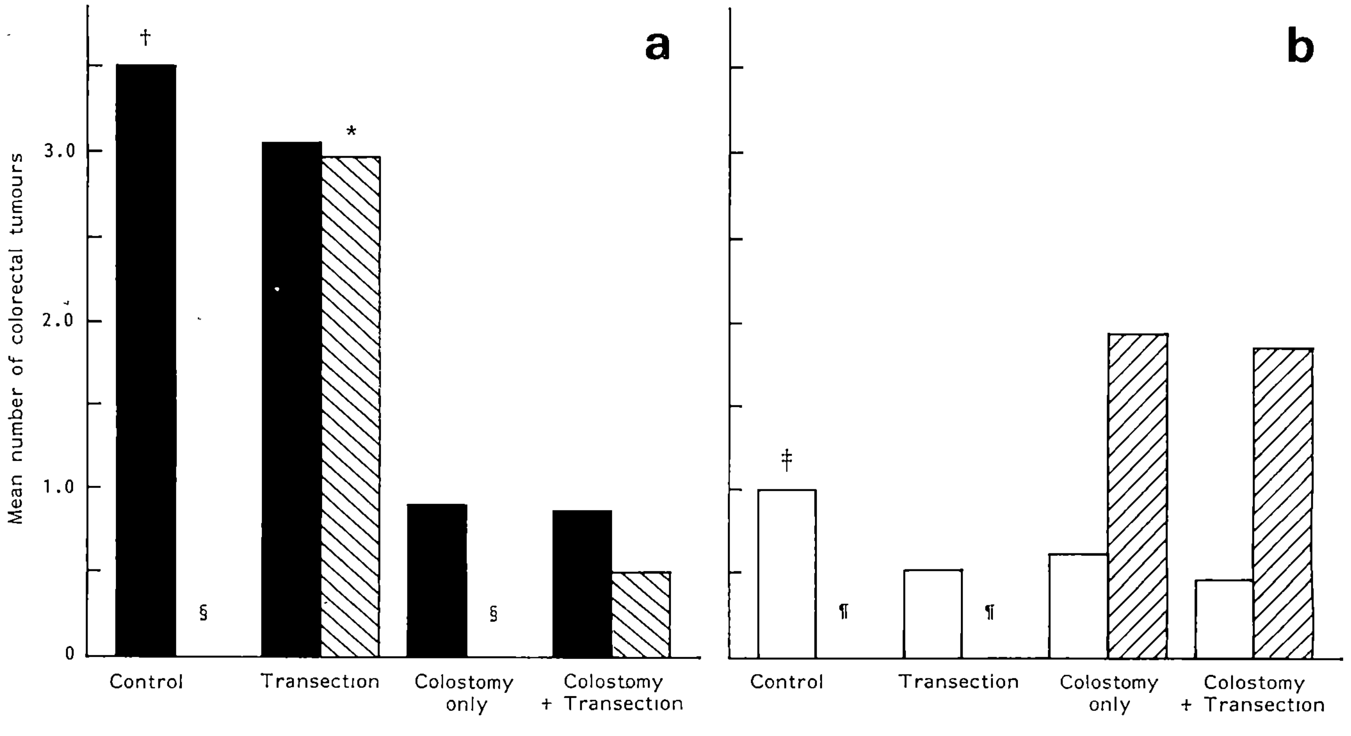

Figure 3 *Colorectal tumour yields mean number of tumours per rat in* **a** *distal (left) colorectum and* **b** *proximal (right) colon* ■, *left-sided tumours excluding anastomosis,* ▧, *anastomotic tumours,* □, *right-sided tumours excluding colostomy,* ▨, *colostomy tumours* * P<0·001 versus *colostomy + transection,* † P<0·001 versus *colostomy only;* ‡ P<0·05 versus *all other tumours;* § *no anastomosis, and* ¶ *no colostomy*

be susceptible to the carcinogen. We have shown that an anastomosis is a very powerful stimulus to malignant change. The presence of a colonic suture line 2–3 mm wide almost doubled the yield of left-sided colonic tumours, an effect similar in magnitude to that of jejunoileal bypass or resection[23,24]

Suture line cancers could reflect the co-carcinogenic effect of chronic irritation by foreign body suture material. A suture placed through the caecal wall becomes the nidus for cancer development[10,25,26]. In rats and perhaps in man the type of suture material may be relevant. Thus, in rats non-absorbable sutures cause more local cancers than rapidly absorbed sutures[10]. Steel wire has an even greater potentiating effect[11], which may extend to the bowel 'downstream' of the anastomosis[10]. Yet the relative lack of anastomotic tumours in defunctioned colon suggests that the rate of cell proliferation is a more important determinant than the presence of sutures.

Anastomotic re-epithelialization takes about 12 weeks in rat colon exposed to azoxymethane[12]. During this time autoradiographic studies have shown a maximum proliferative stimulus immediately adjacent to the anastomosis occurring 2–8 weeks after operation. The present study supports and extends these and other data[15] by demonstrating increased CCPR at the anastomosis at 7 weeks in non-carcinogen treated bowel. The hypoplasia of colonic defunction almost abolished the hyperproliferative effect of an anastomosis, though there was still some clustering of tumours at this site.

Anastomotic hyperplasia may partly explain the high incidence (10–40 per cent) of local recurrence seen after colorectal resection for carcinoma in man[16]. In susceptible colonic mucosa the possibility of a metachronous cancer would surely be higher if CCPR were raised to a similar extent (161 per cent) as seen at the suture line in rats. Our recently published data[27] indicate that colonic defunction dramatically lowers CCPR in the 'normal' human rectum. It is therefore possible that a protective transverse colostomy raised during an anterior resection might lower the incidence of late 'recurrence' at the colorectal anastomosis Perhaps colostomy closure should be delayed for 3 months or so; at this stage in the rat the suture line is cytokinetically stable[12].

The fact that a strong tropic and cancer-promoting stimulus (such as colonic transection) can be almost entirely negated (by defunction) finds a parallel in another recent experiment in our laboratory. Dietary supplementation with calcium reversed the hyperplastic stimulus to colonic mucosa of 80 per cent small bowel resection[28] and subsequently protected against the increased yield of colorectal tumours anticipated in the animals with a shortened gut[29]. These data certainly support our hypothesis that the intensity of cell proliferation is the crucial determinant of the risk of malignant change in the epithelium[9]. The only exception was that right colonic CCPR rose after creation of an end colostomy, whereas tumour yields fell. The right and left colon are known to react differently to carcinogenic stimuli in both man and animals[30,31]. Evidence now favours a predominantly 'genetic' origin for right-sided cancer (e.g familial polyposis), and a 'dietary' origin for left-sided colonic cancer (e.g. fibre and colonic cancer)[31]. Thus dietary or operative manipulation of right-sided cancer may offer less predictable results.

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Stapled Billroth I gastrectomy

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Billroth I reconstruction by stapling can be achieved by transecting the stomach with a transverse stapler and then fashioning the gastroduodenal anastomosis by the use of three transverse staplers. Subsequently circular staplers, inserted either through a separate gastrostomy or retrogradely through the transected duodenum, have been used to perform the gastroduodenal anastomosis. We describe a modification of the technique which lays open the stomach so that the anastomosis is performed by circular stapling through the posterior gastric wall. This technique allows direct visual examination of the completed gastroduodenal anastomosis.

Technique

After routine gastric mobilization the duodenum is divided An 0 Prolene® (Ethicon Ltd , Edinburgh, UK) purse-string stitch is inserted by hand suture around the duodenal stump (*Figure 1*) A Foley catheter is inserted into the duodenum and inflated to dilate the lumen and to prevent the spillage of duodenal contents. The distal stomach is opened along its long axis and the ulcer is visualized The free edges of the stomach are held by either Babcock forceps or stay sutures. The EEA® stapler (US Surgical Corporation, Norwalk, Connecticut, USA) (size 28 or 31 mm) without the anvil is introduced so that the centre rod is pushed through the posterior gastric wall from the mucosal side above the level of the gastric ulcer The anvil is replaced and introduced into the duodenum (*Figure 2*) The Prolene® purse-string is then tied. The gun is fired and the instrument is opened and removed by a combination of rotation and withdrawal The staple line can clearly be seen and is inspected for bleeding points (*Figure 3*) Interrupted sutures of 2/0 Vicryl® (Ethicon Ltd.) are used for haemostasis The TA90® linear stapler (US Surgical Corporation) is then used to close the gastric remnant. The free edges of the diseased stomach are lifted up by stay sutures, the jaws of the TA90 tightened below and the staples are fired. The free gastric edge is excised using a knife (*Figure 4*). Care is taken to allow a gap of 2·5 cm of gastric wall between the circular anastomosis and the linear staple lines to allow an adequate blood supply to each anastomosis (*Figure 5*).

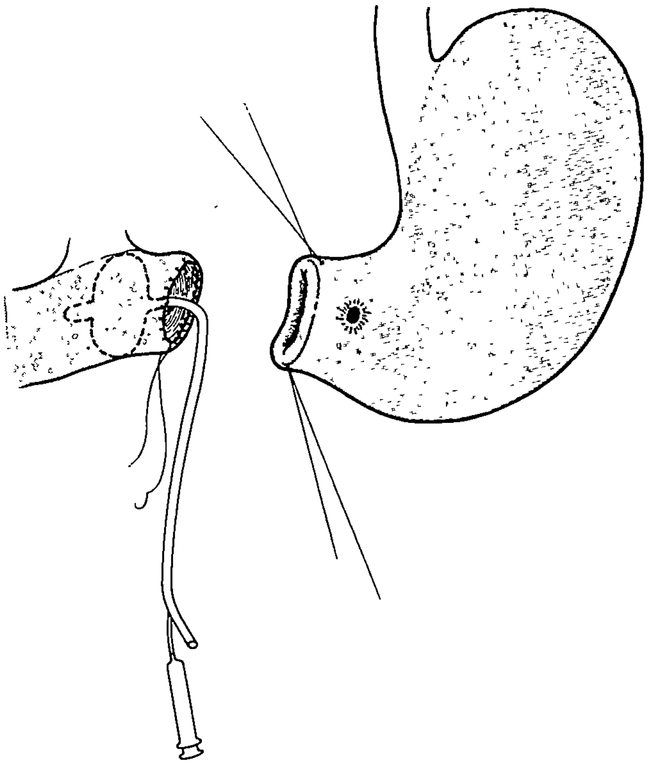

Figure 1 *Purse-string suture inserted and duodenum dilated with a Foley catheter*

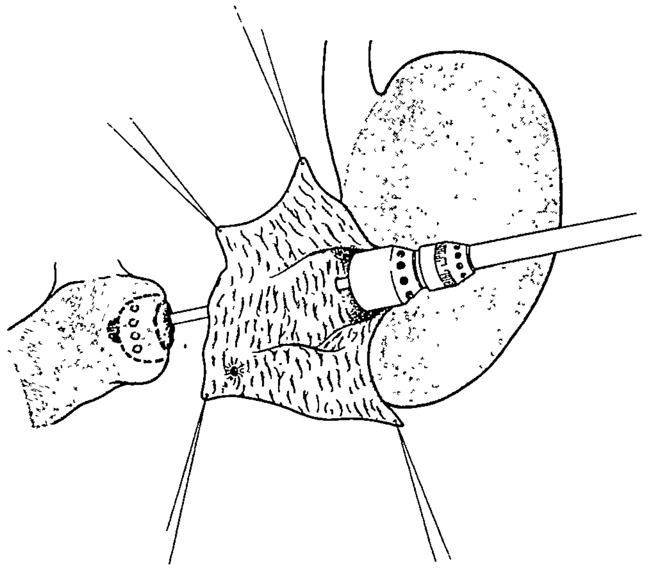

Figure 2 *Distal stomach laid open and EEA® gun inserted through posterior wall*

Discussion

The technique has been used in 28 patients with endoscopically proven benign antral ulcer. The 28-mm stapler was used in four cases and the 31-mm stapler in 24 patients. Complete 'staple rings' were obtained in every case. Twenty-seven patients had

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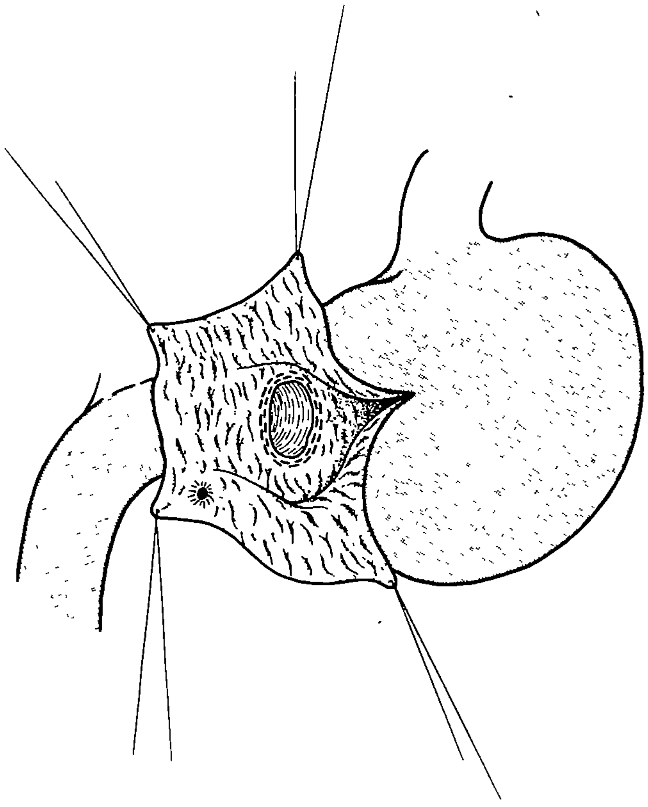

Figure 3 *Gastroduodenal anastomosis inspected for haemostasis*

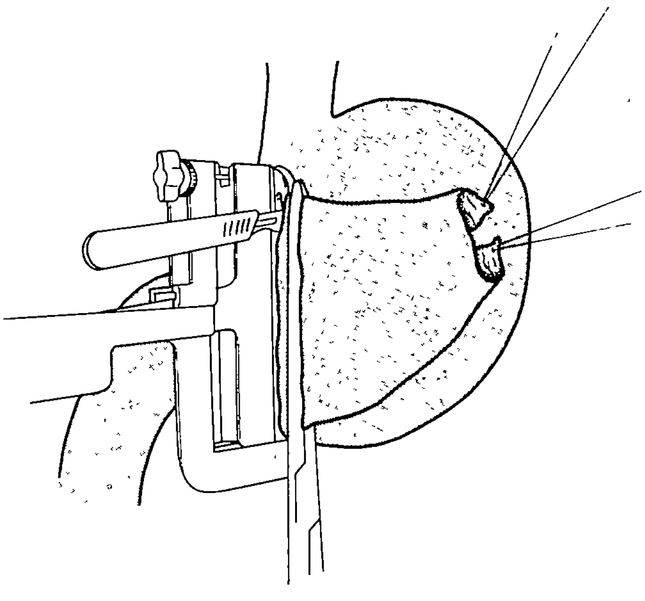

Figure 4 *Distal stomach transected with TA90® stapler*

haemorrhage from the gastroduodenal staple line after removal of the gun, and in seven the bleeding was pulsatile. All 27 patients required manual under-running of the bleeding point for haemostasis. One patient, who had undergone additional suture haemostasis to the staple line, required reoperation for anastomotic bleeding. Median operative blood loss was 250 ml (range 150–400 ml) in electively operated patients and 400 ml (range 250–1000 ml) in emergency cases with ulcer bleeding. Mean operating time was 51 min (range 30–108 min)

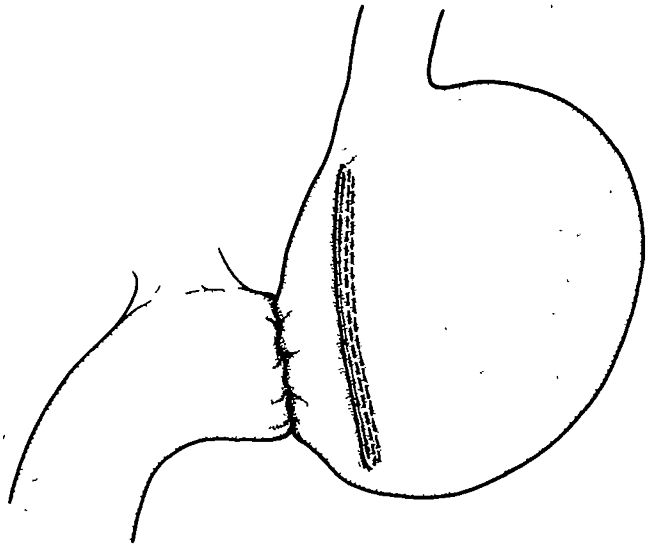

Figure 5 *A gap of 2 5 cm is left between staple lines*

Oral feeding was introduced at 3–6 days after the operation (median 4 days). There were no clinical or radiological anastomotic leakages. There was one wound infection One patient died in hospital after reactivation of pulmonary tuberculosis. Median hospital stay was 10 days (range 7–23 days).

Stapled reconstruction may reduce operating time when compared with hand suturing, a potentially important factor in emergency gastrectomy for bleeding. With the use of the Foley catheter to dilate the duodenum, a size 31-mm EEA® cartridge can be used in most patients so that the resulting stoma is at least as large as those constructed by hand-sewn methods. The improved preservation of mucosal blood flow in stapled anastomoses has to be set against the fact that the staple line is not haemostatic. Inspection of the stapled gastroduodenal suture line for bleeding is therefore an essential step before closing the stomach when using this technique

Anastomotic leakage in hand-sewn Billroth I gastrectomy is rare but may occur at the 'angle of sorrow' where the gastroduodenal anastomosis meets the suture line of the lesser curve reconstruction. The earlier techniques of stapling did not avoid the problem of overlapping suture lines. By stapling through the posterior wall of the stomach with a circular stapler and then transecting the stomach remnant with a TA90® stapler as shown, the angle of sorrow can be eliminated. With this method of stapled reconstruction, there is, however, a narrow strip of stomach between the two staple lines that could become ischaemic We took care to reduce this risk by ensuring that this strip was greater than 2·5 cm and encountered no postoperative problems. This technique of stapled Billroth I reconstruction provides a reliable wide-bore anastomosis with a low incidence of perioperative and postoperative complications.

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Experimental colonic carcinogenesis after gastric surgery

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Peptic ulcer surgery may predispose to the subsequent development of colorectal cancer. This experimental study has investigated the effects of gastric operations on colonic cell proliferation, bile acid excretion and carcinogenesis. Male Sprague-Dawley rats ($n = 105$) *underwent sham operation, Pólya partial gastrectomy or vagotomy and pyloroplasty. The carcinogen azoxymethane was administered weekly for 6 weeks thereafter (total dose 60 mg kg*$^{-1}$*). When the animals were killed 24 weeks after operation, colons were examined for mucosal mass, crypt cell production rate (CCPR) and tumour yield; faeces were assayed for contents of neutral steroids and bile acids (both total and individual). Morphometric indices and mucosal DNA content were similar in all three groups. Pólya gastrectomy reduced: (1) CCPR throughout the colon (by 42–65 per cent,* $P < 0{\cdot}002$*); (2) the number of rats with colorectal tumours (26 per cent* versus *63 per cent,* $P < 0{\cdot}05$*); (3) faecal levels of neutral steroids and bile acids, notably hyodeoxycholic acid* ($P < 0{\cdot}01$)*. Although vagotomy and pyloroplasty increased caecal CCPR, there were no consistent differences in faecal steroids and no alteration in tumour yield after the operation. These results fail to support clinical studies suggesting that gastric surgery predisposes to colonic carcinogenesis. Indeed, Pólya partial gastrectomy exerts a protective effect, probably by inhibiting colonic cell proliferation.*

Keywords: Colonic neoplasms, bile acids and salts

Recent clinical studies suggest that peptic ulcer operations may predispose to the subsequent development of colorectal carcinoma[1–3]. Aetiological factors implicated in colorectal carcinogenesis include dietary fats and sugars[4,5], alterations in colonic bacterial flora[6,7] and changes in bile acid metabolism[8–10].

After partial gastrectomy bile acid metabolism is altered[11], and after vagotomy faecal bile acid excretion is increased[12]. Bile acids can promote experimental colorectal carcinogenesis[13,14], and receptors for secondary bile acids have been located on cytosolic proteins in human colorectal cancer[15]. This study was designed to test the hypothesis that gastric operations may increase the risk of colonic carcinogenesis, perhaps by altering bile acid metabolism.

Materials and methods

Experimental design

One hundred and five male Sprague-Dawley rats weighing 125–150 g were allocated to one of three groups. Group 1 ($n = 35$) had a sham operation consisting of laparotomy with handling of the stomach and colon. Group 2 ($n = 35$) underwent distal hemigastrectomy of Pólya (Billroth II) type (PG), and group 3 ($n = 35$) underwent truncal vagotomy and pyloroplasty (V and P) One week after operation surviving animals received the first of six weekly intramuscular injections of azoxymethane (total dose 60 mg/kg body-weight). The animals were regularly examined for evidence of tumour development and were killed at 24 weeks or earlier if moribund. At autopsy the entire gastrointestinal tract was excised and flushed with ice-cold saline to remove all content The gastrointestinal tract was opened longitudinally in a tray resting on crushed ice, and any tumours were identified and recorded The length and wet weight of the colon and rectum were measured together with the weight and surface area of the caecum. Similar samples of descending colon were taken for mucosal DNA estimation, and any tumours were excised and prepared for histological examination. Faeces were removed from the rectum immediately after sacrifice and stored at −40°C for later analysis of faecal steroids.

Six rats in each group received the stathmokinetic agent vincristine sulphate (1 mg kg^{-1} intraperitoneally) Animals were killed sequentially at 30 min intervals from 30 to 180 min after injection of vincristine At autopsy segments of caecum, ascending colon and descending colon were excised and fixed in Carnoy's solution for subsequent estimation of crypt cell production rate (CCPR).

Analyses

CCPR Specimens were stained with Schiff's reagent by Feulgen's method. On a glass slide, under the dissecting microscope, the mucosa was teased from the submucosa and individual crypts were dissected out A drop of 45 per cent acetic acid was applied, and the crypts were gently squashed under a coverslip The slide was transferred to a light microscope for examination Arrested metaphases in each crypt were counted and the mean of counts from ten individual crypts was taken as the value for that specimen at that time Crypt cell production rate was determined by calculating the slope of the line best fitting the six individual points thus obtained by linear regression analysis.

DNA content DNA was measured by a simplified method first described by Scott *et al*[16] and modified by Hinrichs *et al.*[17], which relies upon alkaline digestion to separate the two nucleic acids. Aliquots of frozen, weighed, homogenized specimens were treated with ice-cold alcoholic 0·1 M potassium acetate and then with absolute alcohol for 30 min at 60°C. After overnight drying at 37°C, pellets were dissolved in 1 M potassium hydroxide at 85°C DNA was measured fluorimetrically by a modification of the method of Kissane and Robins[18], which is specific for this compound.

Faecal steroids Steroids were assayed by a previously described method[19]. After freeze-drying the faecal samples were ground to a fine homogeneous powder and 500 mg of the dry sample was continuously extracted using chloroform:methanol (1:1) for 6 h in a Soxhlet apparatus The extract was fractionated by anion-exchange column-chromatography on diethylamino-hydroxypropyl-Sephadex (DEAP-LH-20) into three fractions. (1) neutral steroids, (2) free bile acids and (3) glycine and taurine amidates and sulphated steroids The neutral steroids and free bile acid fractions were analysed by gas–liquid chromatography as previously described[19] The fraction containing bile

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acid amidates and sulphated steroids was first desulphated by solvolysis as described by Alme *et al* [20]. Then deconjugation was carried out by dissolving the sample in 1·0 ml 20 per cent potassium hydroxide dissolved in ethylene glycol and heating at 120°C for 2 h, 1·0 ml of methanol and 9·0 ml 20 per cent aqueous sodium chloride were added prior to acidification with 6 N HCl. The acidified sample was extracted twice with an equal volume of diethyl ether and the resultant extract was derivatized and analysed by gas–liquid chromatography[19]

Statistical analysis

Statistical analysis of the results was performed using the Kruskal Wallis analysis of variance, the Mann–Whitney *U* test and Student's *t* test. Differences in the numbers of gastrointestinal tumours were evaluated by the χ^2 test

Results

Mortality rate

Fourteen (13 per cent) rats died before the end of the first week after operation from haemorrhage, anaesthetic overdose or anastomotic dehiscence. Another 19 (21 per cent) of the remaining 91 animals died before completion of the experiment. Post-mortem examination often revealed no obvious cause of death. In the animals with V and P, gastric distention suggested that postvagotomy gastric atony may have been a contributory factor. There were no premature deaths from carcinomatosis. Overall, 72 (69 per cent) animals survived until killing, including 24 out of 30 controls, 31 out of 31 with partial gastrectomy and 17 out of 30 with V and P (denominations represent those animals surviving postoperative period)

Body-weight

Within 2 weeks of operation initial body-weight had been regained in all three groups. Throughout the experiment controls consistently weighed more than those with gastric operations, and animals with PG consistently weighed more than those with V and P. At killing the median weight of the PG group (563 g, range 381–718 g) was 4 per cent less than that of controls (586 g, range 417–709 g; n.s.), while the V and P group weighed 13 per cent less (508 g, range 432–604 g; $P=0{\cdot}0007$) than controls. Animals with V and P also weighed less than animals with PG ($P=0{\cdot}02$).

Colonic adaptation (Table 1)

The wet weight of the colon was 13 per cent lower than control values after either PG or V and P ($P<0{\cdot}01$). For the caecum there was no significant difference in wet weight between groups. Colorectal length was similar in all three experimental groups. Caecal surface area was similar in controls and animals with PG, but was 14 per cent and 11 per cent less in animals with V and P compared with PG and control animals respectively. Colonic mucosal DNA was lowest in the PG and highest in the V and P groups, although these differences did not achieve statistical significance.

Crypt cell production rate (Figure 1)

In the caecum PG reduced CCPR by 65 per cent compared with controls and by 77 per cent compared with V and P. V and P increased caecal CCPR by 49 per cent compared with controls. Likewise in the right colon PG reduced CCPR by 54 per cent compared with controls and by 45 per cent compared with V and P. There was no significant difference in CCPR between controls and those with V and P In the descending colon PG reduced CCPR by 42 per cent compared with controls and by 20 per cent compared with V and P, but these differences did not reach statistical significance.

Gastrointestinal tumours

Of 24 control animals 15 (63 per cent) developed one or more colonic tumour compared with 13 of 17 (76 per cent) with V and P ($\chi^2=0{\cdot}36$; n.s) and 8 of 31 (26 per cent) with PG ($\chi^2=6$, $P<0{\cdot}05$). There were markedly fewer animals with tumours in the PG group compared with the V and P group ($\chi^2=9{\cdot}48$;

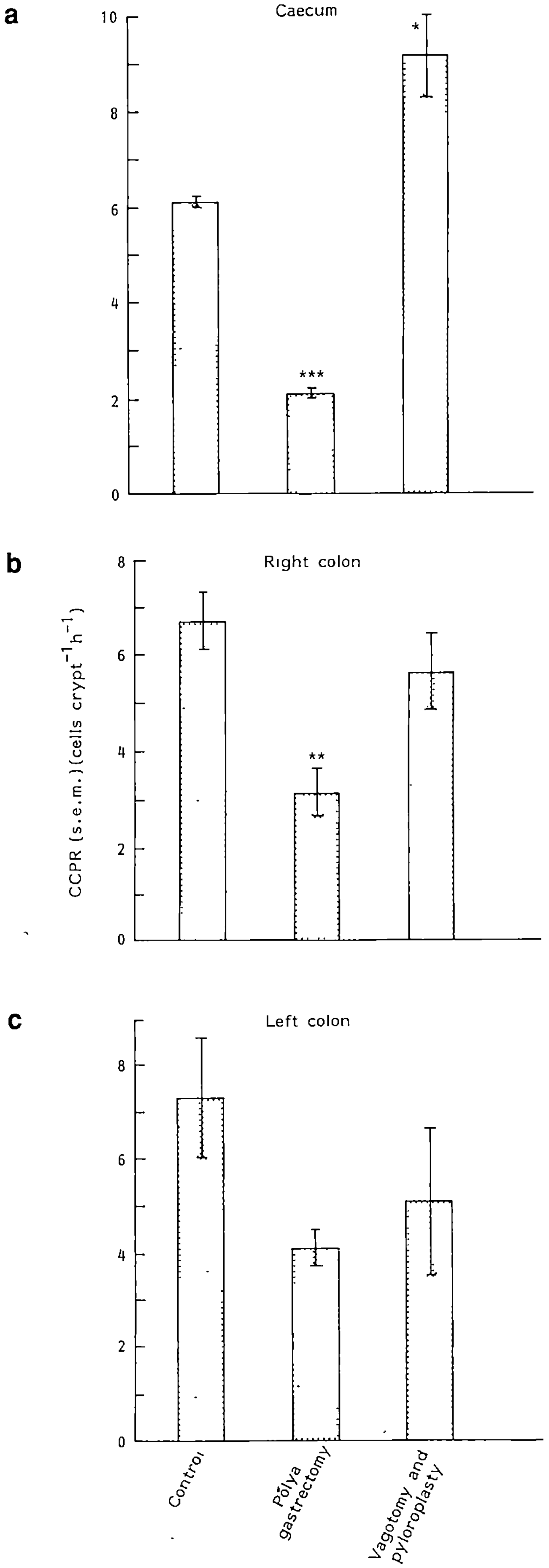

Figure 1 *Mean(s.e.m.) crypt cell production rates in large-bowel mucosa 24 weeks after operation,* **a** *caecum,* **b** *right colon and* **c** *left colon* *P<0·05, **P<0·002; ***P<0·001 (*Student's t test*)

Table 1 *Indices of colonic adaptation*

	Group*			Statistical significance†		
	Control (1)	Pólya gastrectomy (2)	Truncal vagotomy and pyloroplasty (3)	(1) *versus* (2)	(2) *versus* (3)	(1) *versus* (3)
Colon						
Wet wt (g)	3·0 (2·3–4·4)	2·6 (2·0–3·7)	2·6 (1·8–3·0)	0·01	n s.	0·003
Length (cm)	24 (18·5–30·5)	23·5 (20–31)	23 (19–25)	n.s	n.s	n.s.
DNA (μg/cm^2)	490 (264–1155)	473 (140–916)	528 (207–1240)	n.s.	n.s	n s
Caecum						
Wet wt (g)	1·8 (1·4–2·6)	1·8 (1·3–2·9)	1·8 (1·5–2·4)	n.s.	n.s	n s
Surface area (cm^2)	31 (23–40)	32 (20–36)	27·5 (19–36)	n s.	0·001	0·009

* Median (range in parentheses), † Mann–Whitney *U* test

Table 2 *Faecal neutral steroid levels*

	Group*			Statistical significance†		
Steroid	Control (1) ($n=17$)	Pólya gastrectomy (2) ($n=22$)	Vagotomy and pyloroplasty (3) ($n=11$)	(1) *versus* (2)	(2) *versus* (3)	(1) *versus* (3)
Coprostanol	0·89 (0·23–2·58)	0·61 (0·35–1·90)	0·95 (0·61–4·39)	n.s	0·006	n s.
Cholesterol	1·05 (0·66–1·74)	0·80 (0·53–1·59)	0·89 (0·68–3·09)	0·003	n s.	n.s
Total animal sterols	1·87 (1·20–4·32)	1·39 (0·98–3·49)	1·77 (1·33–7·48)	0·007	0·01	n.s
Percentage coprostanol	44 (15–60)	43 (32–55)	49 (35–61)	n.s.	0·02	n s
Total plant sterols	6·00 (3·63–9·41)	4·36 (2·40–9·04)	5·07 (3·07–16·78)	0·005	n s.	n s.
Total sterols	7·83 (5·12–13·73)	5·72 (3·38–12·58)	6·81 (4·40–24·26)	0·005	n s.	n s
Percentage plant sterols	75 (69–83)	77 (62–82)	70 (65–79)	n.s.	0·01	0·03
Cholesteryl sulphate	0·11 (0·07–0·19)	0·09 (0·06–0·32)	0·11 (0·07–0·37)	n.s.	n.s	n.s

* Median (range in parentheses) in mg/g dry faeces unless otherwise stated, † Mann–Whitney *U* test

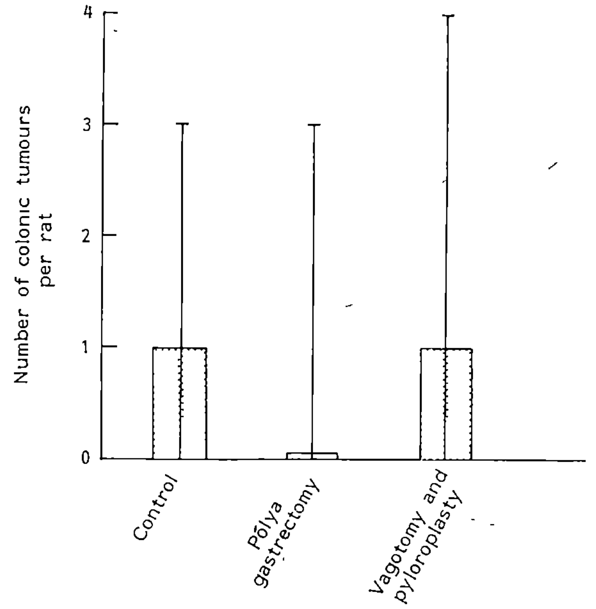

Figure 2 *Numbers of large-bowel tumours per rat in each operative group (median values with range).*

$P<0\cdot01$). The number of colonic tumours per rat also varied between experimental groups (*Figure 2*). Yields were higher in controls (median 1, range 0–3; $P=0\cdot02$) and rats with V and P (median 1, range 0–4; $P=0\cdot006$) than in those with PG (median 0, range 0–3). There was, however, no significant difference in tumour numbers between controls and rats with V and P. The pattern of colorectal tumour distribution was similar in the three experimental groups. Although V and P caused more proximal lesions and PG more distal lesions than in controls, these differences were not statistically significant.

Faecal steroid levels

Faecal levels of neutral steroids were lower after PG (*Table 2*). Compared with controls, faeces contained significantly less cholesterol, total animal sterols, total plant sterols and total sterols. Compared with V and P, faeces contained less coprostanol and total animal sterols. Levels in controls and rats with V and P were similar. Similarly, faecal levels of bile acids were lower in rats with PG than in either of the other two groups (*Table 3*) In particular, there were lower levels of hyodeoxycholic acid and total bile acids. Again very few differences could be discerned between control rats and those with V and P, though levels of deoxycholic acid were higher in the V and P group than in the other two groups

Discussion

No evidence was found that gastric operations promote experimental colorectal carcinogenesis. On the contrary, Pólya partial gastrectomy appears to have a protective role, with both fewer tumour-bearing animals and fewer tumours per rat. These data concur with a previous clinical study showing that patients undergoing partial gastrectomy for gastric or duodenal ulcers have a lower incidence of colorectal cancer than expected up to 20 years after operation[21].

Partial gastrectomy had a generally suppressive effect on the colonic mucosa with reductions in mucosal mass (wet weight) and CCPR throughout the colon Vagotomy and

Table 3 *Faecal bile acid levels*

	Group*					
				Statistical significance†		
Bile acid	Control (1) ($n=17$)	Pólya gastrectomy (2) ($n=22$)	Vagotomy and pyloroplasty (3) ($n=11$)	(1) *versus* (2)	(2) *versus* (3)	(1) *versus* (3)
Lithocholic acid	0·04 (0·03–2·74)	0·05 (0·01–0·08)	0·02 (0·01–0·03)	n.s.	n.s.	n.s.
Deoxycholic acid	0·51 (0·08–1·57)	0·42 (0·03–1·58)	1·03 (0·33–2·96)	n.s.	0·004	0·02
Chenodeoxycholic acid	0·10 (0·08–0·23)	0·08 (0·04–3·07)	0·13 (0·07–0·34)	n.s.	n.s.	n.s.
Hyodeoxycholic acid	0·82 (0·05–2·39)	0·45 (0·04–1·52)	0·92 (0·22–1·88)	0·03	0·04	n.s.
Cholic acid	0·12 (0·03–0·76)	0·15 (0·02–2·44)	0·31 (0·01–0·90)	n.s	n.s.	n.s
Muricholic acid‡	0·21 (0·11–1·06)	0·14 (0·04–1·14)	0·13 (0·04–1·14)	n.s.	n.s.	n.s.
Total free bile acids	2·08 (0·45–4·85)	1·14 (0·11–7·97)	2·45 (0·63–6·54)	n.s.	0·009	n.s.
Total amidates§	0·10 (0·04–0·50)	0·06 (0·04–0·73)	0·14 (0·03–0·75)	n.s.	n.s.	n.s.
Total bile acids	2·17 (0·49–5·24)	1·24 (0·16–8·13)	2·59 (0·75–6·76)	0·05	0·006	n.s.

* Median (range in parentheses) in mg/g dry faeces, † Mann–Whitney U test; ‡ Including α and β muricholic acid; § Bile acids conjugated to either glycine or taurine

pyloroplasty had a much less marked effect, a reduction in caecal surface area being balanced by an increased CCPR. Mucosal DNA content should provide a more accurate assessment of mucosal mass than simple morphometry, but in this study the wide experimental error precluded any reduction from being detected as significant. It seems logical to attribute the inhibitory effect of partial gastrectomy on carcinogenesis to its hypoplastic effect on the colonic mucosa, since there is a close correlation between the proliferative status of the large bowel and its susceptibility to chemical carcinogens[22]. However, changes in faecal bile acids and circulating gastrin levels must also be considered.

Several studies using this experimental model have indicated a cocarcinogenic role for bile acids in the large bowel[13,14]. Bile acids might be converted to carcinogenic substances by bacterial action or merely stimulate cell proliferation by means of direct mucosal irritation. Thus the reduced faecal content of bile acids seen after partial gastrectomy is consistent with the lower tumour yield observed in this group of animals. Hyodeoxycholic acid, the major bile acid in rat faeces, was particularly low.

Resection of the gastric antrum produces hypogastrinaemia. Although gastrin is tropic to gastric mucosa[23], its effect on the colon remains controversial. Oscarson *et al* [24] found no alteration in colonic tumour yields in rats having either gastric fundectomy (inducing hypergastrinaemia) or antrectomy, yet gastric receptors have been found in colon cancer[25] and gastrin stimulates colon cancer in mice[26]. Vagotomy is known to increase circulating levels of gastrin, and the largest number of tumours was found in this group. Although this increase was not statistically significant, perhaps because of the associated weight loss, it does provide some support for the hypothesis that gastrin may have a mediating influence on colonic carcinogenesis. Weight loss can prevent the adaptive response of the gut, but V and P did not cause significant hypoplasia (caecal CCPR was actually increased). The modest (13 per cent) weight loss in this group might have blunted a small effect on the gut, but not a major effect. Thus, when the adaptive stimulus is strong enough (jejunoileal bypass) the colon develops hyperplasia and enhanced neoplasia despite much more extensive (27 per cent) loss of body-weight[27]. Truncal vagotomy also increases faecal bile acid excretion, especially with respect to deoxycholic acid[12], as confirmed for the V and P group in the present study. If bile acids are involved in colonic carcinogenesis after gastric surgery, one might anticipate an increase in proximally sited tumours, as after cholecystectomy[28]. Caecal CCPR was increased after V and P and there was a trend towards more proximal tumours.

Extrapolation of animal experiments to man must always be tempered with caution. It may be that this animal model is inappropriate to determine the long-term effect of gastric surgery on colonic carcinogenesis. Nevertheless, we have not confirmed an increased risk of colorectal cancer after gastric operations; rather we have observed some short-term protection afforded by Pólya gastrectomy.

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Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases

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Survival benefit from hepatic artery embolization (HAE) or hepatic arterial infusion chemotherapy (HAI) in patients with unresectable colorectal liver metastases has not previously been assessed in a randomized controlled trial. Sixty-one patients were randomized, 20 to receive no treatment, 22 to receive HAE, and 19 to receive HAI with 5-fluorouracil and degradable starch microspheres. Both treatments were acceptable to the patients in terms of low treatment morbidity rate. Median survival from diagnosis of metastases was 9·6 months for controls, 8·7 months for the HAE group and 13·0 months in the HAI group. There was no apparent survival benefit for the HAE group. The increased survival in the HAI group was observed in all the subgroups analysed but failed to reach statistical significance. The greatest observed benefit was achieved in the subgroup with <50 per cent hepatic replacement with tumour at presentation (median survival from diagnosis 10·0 months for controls, 10·2 months for HAE and 23·6 months for HAI); 36 per cent of patients developed extrahepatic disease recurrence. No significant benefit has been shown from either HAE or HAI, but a more carefully selected group of patients with only low volume hepatic disease may benefit from HAI therapy.

Keywords: Colorectal neoplasms, liver metastases, hepatic artery, treatment, microspheres, embolization

Up to 50 per cent of patients with colorectal cancer develop liver metastases which may be either synchronous or metachronous[1]. The natural history depends on the extent of disease at presentation, but the overall median survival of untreated metastases is of the order of 9–10 months. As these patients are frequently asymptomatic for the majority of this time, prolonged survival would be worthwhile if any treatment given was acceptable to the patient. A variety of therapeutic options are available but treatment remains a controversial issue.

The role of hepatic resection for colorectal liver metastases has recently been reviewed[2] and is probably associated with improved survival in a carefully selected group. There remains a large group of patients with unresectable liver metastases and numerous studies of systemic chemotherapy have failed to prove any significant survival benefit. In view of the predominant arterial blood supply to liver metastases it was only logical that therapeutic attempts should turn to hepatic artery perfusion.

Response rates of 90 per cent are associated with long-term hepatic arterial infusion chemotherapy[3,4], but are meaningless unless associated with survival gain. Hepatic artery embolization has also been reported to be of value[5,6]. Neither of these treatment options has been assessed in a randomized controlled trial to determine survival benefit. More recently attention has been given to the use of degradable starch microspheres (DSM) in conjunction with hepatic arterial chemotherapy. DSM cause a temporary blood flow stasis resulting in enhanced regional uptake of chemotherapeutic agents and reduction in systemic toxicity[7–9].

We report a randomized controlled trial to assess the morbidity and any survival benefit from hepatic arterial embolization or hepatic arterial infusion chemotherapy with DSM in patients with unresectable colorectal liver metastases.

Patients and methods

Eighty-three patients were referred for consideration for entry into the trial. All were assessed by clinical examination, chest radiograph, isotope liver scan, abdominal ultrasound and computed tomographic (CT) imaging Laparotomy was carried out when indicated An estimate of the percentage hepatic replacement with tumour was made

Patients were eligible for inclusion in the trial if they fulfilled the following inclusion criteria:

1 Unresectable colorectal liver metastases confirmed by histology or a combination of imaging techniques
2 Age 18–75 years
3 Karnofsky score >60
4. No evidence of extrahepatic disease
5. Patients fit enough to undergo laparotomy
6. Patients who agreed to be included in a clinical trial after informed consent

Patients were excluded if extensive disease was evident by the presence of jaundice or ascites or if the percentage hepatic replacement with tumour was greater than 75 per cent.

Sixty-one patients were eligible for the trial, 20 were randomized to the control arm, 22 to receive hepatic artery embolization (HAE) and 19 to receive hepatic artery infusion chemotherapy (HAI) Twenty-two patients were excluded prior to randomization as shown in *Table 1*.

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Table 1 *Details of patients included and excluded from the trial* (n = 83)

Patients excluded (*n*=22)		Patients included (*n*=61)	
Lung metastases	6	Control	20
Jaundiced	4	Embolization (HAE)	22
Ascites	3	Infusion (HAI)	19
Unresectable primary	2		
Hepatic resection	4		
Refused trial	1		
No tumour	1		
Benign disease	1		

The study group consisted of a total of 43 men and 18 women Forty-two had synchronous metastases and 19 had metachronous metastases, 11 of which were diagnosed on routine follow-up investigations and were asymptomatic. Eight patients had symptomatic metachronous metastases, of whom two were randomized to the control arm and three each to HAE and HAI There were no significant differences between the groups for age, sex, primary carcinoma site, Dukes' staging or histology of the primary tumour, proportion of synchronous or metachronous metastases or the percentage hepatic replacement with tumour stage.

Further management of trial patients

Control arm. These patients had no active therapeutic intervention, although symptomatic treatment was provided whenever necessary.

Hepatic artery embolization All patients in this group underwent hepatic arteriography. Selective coeliac and superior mesenteric angiograms were obtained to observe the hepatic arterial anatomy. Selective splenic artery cannulation was performed to establish patency of the portal vein

Embolization was performed by selective cannulation of the main hepatic artery or right and left hepatic arteries when possible, dependent on the arterial anatomy. Embolization was performed with homologous lyophilized dura mater (Lyodura®, Braun Melsungen, Melsungen, FRG) to occlude smaller peripheral vessels, and Gelfoam (Sterispon®, Allen and Hanburys Ltd., Greenford, UK) to occlude the larger proximal arterial branches. Finally arteriography was performed to ensure that complete embolization was achieved

Hepatic arterial chemotherapy. The patients in this group also had hepatic angiography performed to define the arterial anatomy prior to operative insertion of a Port-A-Cath® arterial delivery system (Pharmacia Ltd , Milton Keynes, UK)

At laparotomy the opportunity was taken to ensure no extrahepatic disease was evident. The Port-a-Cath catheter was introduced via an arteriotomy in the gastroduodenal artery and inserted up to the origin of the gastroduodenal artery from the hepatic artery. If anomalous hepatic arterial vessels were present on the arteriogram and could be identified at operation, they were ligated

Intra-arterial chemotherapy regime

The first treatment course comprised four injections on consecutive days, and each subsequent course consisted of two injections on consecutive days performed every 28 days Each injection was the same and comprised 500 mg 5-fluorouracil (5-FU) mixed with 300–900 mg DSM (Pharmacia Ltd.). Each injection was followed by a heparinized saline flush The initial patients all had 900 mg DSM given on each occasion but subsequently DSM monitoring has been employed during the first treatment course and an appropriate DSM dosage determined on an individual basis[10]. The dose of 5-FU used was relatively low but was based on a previous study indicating that the addition of DSM doubles the drug concentration within tumour[11].

In the interval between each monthly treatment the system was again flushed with heparinized saline. The patency and perfusion distribution of the cannula was checked by injection of radiolabelled macroaggregated albumen and periodically this was repeated to ensure continued cannula patency and hepatic perfusion.

Results

Treatment acceptability

Hepatic artery embolization. Of 22 patients randomized to receive HAE six had anatomical variations of the hepatic arterial tree. Of these two had a 'normal' hepatic arterial anatomy but arising from the superior mesenteric artery – one was successfully embolized and the other proved technically impossible. Two had an aberrant right hepatic artery from the superior mesenteric artery – one of these had complete embolization of the right and left arteries and the other, with right-sided metastases only, had successful embolization of the aberrant right hepatic artery only. One patient had an aberrant left hepatic artery arising from the left gastric artery, and both the 'normal' right hepatic artery and aberrant left hepatic artery were embolized. The final patient had a complete coeliac occlusion with arterial collaterals not amenable to embolization The remaining 16 patients had normal hepatic arterial anatomy and 15 of these had successful complete embolization (one failed).

In all, 18 complete embolizations were performed, one partial embolization of the right hepatic artery only, and in three cases attempted embolization failed. The failed cases have been included in the analysis of the HAE arm in accordance with the accepted practice of analysing results on an 'intention to treat' basis.

There were no major complications associated with the procedures. One patient developed a local puncture site haematoma, and all the patients with successful embolization developed features of the 'post-embolization syndrome'. This comprised pain, nausea, vomiting and pyrexia. No patient required more than symptomatic treatment and symptoms lasted for between 1 and 5 days only

Hepatic arterial infusion. As in the HAE group, six arteriographic abnormalities were demonstrated. One had the entire hepatic arterial circulation arising from the superior mesenteric artery and normal cannulation was achieved Four patients had an aberrant right hepatic artery arising from the superior mesenteric artery – two of these had left hepatic artery perfusion achieved via gastroduodenal artery cannulation combined with right hepatic artery ligation and two failed attempted cannulation. One patient had an aberrant left hepatic artery arising from the left gastric artery in whom only right hepatic artery perfusion was achieved after gastroduodenal artery cannulation.

In total 14 patients achieved complete perfusion following cannulation, three achieved only partial hepatic perfusion, and two failed attempted cannulation. The patients with failed cannulation have again been included in the analysis.

One patient developed a wound infection and another a deep vein thrombosis. Treatment sessions were well tolerated. All patients developed nausea with or without vomiting immediately after most of the hepatic arterial injections of 5-FU with DSM. This was only short-lived, lasting between 30 and 60 min. Pain or discomfort was also occasionally experienced, but was equally short in duration. No alopecia, haematological toxicity or other side effects have been observed.

In the patients with successful cannulation, 2–34 monthly treatments were received (median 7). The major problem associated with the arterial cannulae has been occlusion. Port-a-Cath occlusion or fracture occlusion has occurred in eight patients at 3, 3, 4, 4, 5, 6, 7 and 34 months. In three patients with early catheter occlusion (3, 3 and 4 months), arteriography confirmed patent hepatic arterial vessels, and a second Port-a-Cath was inserted directly into the hepatic artery with proximal arterial ligation. Further 5-FU chemotherapy without DSM could then be given for an additional 7 and 12 months in two patients before occlusion again occurred. The third patient continues to receive monthly 5-FU 12 months after the first catheter occluded.

Survival

Logistic problems prevented serial computed tomographic scan measurements to assess response rates in this trial, and emphasis was placed on survival as the important end-point.

Patients have been followed for a minimum of 7 months.

Nineteen of the 20 control subjects, 19 of the 22 HAE patients and 15 of the 19 HAI patients have died. The median survival times for each group are shown in *Table 2*. There is a slight survival advantage for the HAI group, but the overall results fail to reach statistical significance using the log rank test ($\chi^2=2{\cdot}43$, d.f. $=2$, $P=0{\cdot}30$ for survival from trial entry; $\chi^2=3{\cdot}85$, d.f. $=2$, $P=0{\cdot}15$ from diagnosis). The HAE arm offered no survival benefit.

Using Cox's proportional hazards model, several characteristics have been investigated for an independent association with risk of death (*Table 3*) based on survival from trial entry. Age ($P=0{\cdot}006$), the percentage hepatic replacement with tumour staging ($P<0{\cdot}001$), and original Dukes' staging of the primary lesion ($P<0{\cdot}001$) showed a significant association. The odds ratio of death for the HAI group was 0·63 (95 per cent confidence interval 0·32–1·26).

Subgroup analysis might show a significant benefit for one of the treatment arms for a specific subgroup. Patients with synchronous or metachronous metastases and patients with <50 per cent hepatic replacement with tumour or >50 per cent hepatic replacement with tumour have been analysed separately (*Table 4*) The median survival is longest in the HAI group in all cases, but no significant benefit has been demonstrated for any of these subgroups. The small numbers in each subgroup limit the sensitivity that can be expected.

Development of extrahepatic disease

The aim was to exclude patients with extrahepatic disease as assessed by a combination of clinical examination, chest radiography, ultrasound and computed tomographic imaging and/or laparotomy. Inevitably some patients did develop either local recurrence or other distant metastases. In all, 22 patients developed evidence of extrahepatic disease, five out of 20 (25 per cent) in the control arm, nine out of 22 (41 per cent) in the HAE arm and eight out of 19 (42 per cent) for HAI. Ten patients developed local recurrence, seven of whom also had evidence of peritoneal, lung or bone metastases and 12 apparently developed extrahepatic metastases without local recurrence.

Table 2 *Median survival (range) in months for each group*

	Trial entry	Diagnosis
Controls	7·9 (1–26)	9·6 (1–27)
HAE	7·0 (2–44)	8·7 (2–49)
HAI	10·7 (3–38)	13·0 (3–38)

Table 3 *Cox's proportional hazards model for risk of death*

	Odds ratio	*P* value
HAE	0·85	–
HAI	0·63	–
Age	1·05	0·006
Sex (female)	1·84	0·07
Dukes' (C *versus* A/B)	4·65	<0·001
Percentage hepatic replacement with tumour stage	2·48	<0·001
Synchronous (*versus* metachronous)	0·76	0·40

Discussion

There has been a great deal of interest in hepatic arterial infusion chemotherapy and DSM offers potential advantages to enhance this route of therapy. At the initiation of this trial there was also particular interest in the development of hepatic arterial embolization as potential therapy for liver metastases. In previous studies there has been a marked emphasis on response rates rather than survival and a lack of randomized controlled trials. This is the first randomized trial to assess survival benefit from hepatic arterial chemotherapy with DSM, or HAE, compared with an untreated control group.

It is important that treatment options should be well tolerated with a low complication rate, particularly when the aim is to improve survival but not cure disease. To this extent both hepatic artery embolization and infusion chemotherapy have been acceptable. There were no major side effects and the minor side effects and complications reported were short-lived and self-limiting.

Anatomical variations in hepatic arterial anatomy occurred in 29 per cent (12 of 41) of patients. Although four of five failed treatments occurred in patients with such abnormalities, the overall complete or partial treatment rate (36 of 41) is acceptable. The most worrying feature of the HAI treated group was the early failure rate of the arterial catheters despite regular heparinized saline flushes. Seven catheters occluded within 7 months of insertion. Although three of these were reinserted, this obviously involves repeat arteriography and laparotomy with the increased risk of morbidity and patient discomfort.

It is apparent from the median survival times (*Tables 2* and *4*) that no survival benefit is achieved from HAE. Interpretation of the data for the HAI arm is more difficult. The overall median survival for HAI from trial entry was 10·7 months compared with 7·9 months for controls, and from diagnosis of metastases 13·0 months compared with 9·6 months for controls. This may be a small but real difference but the relatively low numbers in each group prevent statistical significance from being reached. This possibility is supported by the fact that each subgroup analysed (metachronous or synchronous metastases, >50 per cent hepatic replacement with tumour and <50 per cent hepatic replacement with tumour) showed a higher median

Table 4 *Median survival times (range) for each subgroup in months.* P *values by log rank test for survival in each case*

			From trial entry		From diagnosis	
		n	Survival	*P*	Survival	*P*
Synchronous metastases:	Control	16	10·0 (1–26)		10·2 (1–27)	
	HAE	12	6·8 (2–44)	0·49	8·7 (2–45)	0·26
	HAI	14	10·7 (3–38)		12·9 (3–38)	
Metachronous metastases:	Control	4	5·2 (3–7)		6·2 (5–9)	
	HAE	10	8·1 (2–44)	0·17	9·7 (3–49)	0·09
	HAI	5	10·2 (5–23)		11·3 (6–26)	
<50 per cent hepatic replacement with tumour:	Control	13	8·2 (3–26)		10·0 (5–27)	
	HAE	12	9·3 (4–44)	0·18	10·2 (5–49)	0·16
	HAI	13	21·5 (4–38)		23·6 (6–38)	
>50 per cent hepatic replacement with tumour:	Control	7	7·6 (1–22)		8·5 (1–22)	
	HAE	10	4·7 (2–14)	0·80	6·8 (2–15)	0·50
	HAI	6	7·9 (3–10)		9·9 (3–33)	

survival in the HAI treated group, although none reached statistical significance. The maximum difference was observed in patients with <50 per cent hepatic replacement with tumour where the HAI group had a median survival of 21·5 months from trial entry compared with 8·2 and 9·3 months for the controls and HAE group respectively (*Table 4*). It is well established that the percentage hepatic replacement with tumour is a significant prognostic factor and it therefore seems reasonable that the most likely group to be influenced with regard to survival is that with low volume disease.

Randomized studies have been remarkably rare. One compared hepatic artery infusion against intravenous infusion of 5-FU in 74 patients with colorectal liver metastases and no evidence of extrahepatic disease[12]. Unfortunately the arterial infusion group only received one 3-week course of arterial therapy followed by the same subsequent intravenous therapy in both groups. The response rate in the arterial therapy group (34 per cent) was not significantly higher than the intravenous only group (23 per cent). The preliminary results of another randomized study of hepatic arterial *versus* intravenous infusion of 5-fluorodeoxyuridine (5-FUDR) in 50 patients showed a response rate of 43 per cent compared with 33 per cent[13]. Survival figures cannot be interpreted because of crossover between the two treatment groups. More recently a similar but non-crossover randomized study of arterial *versus* intravenous infusion of 5-FUDR has been reported in patients with no extrahepatic disease other than hepatic nodal or aortic nodal involvement[14]. The response rate in the arterial group was significantly higher (62 per cent *versus* 17 per cent), but this was not translated into a significant survival benefit Those treated with arterial therapy who had no known nodal involvement did survive significantly longer than node negative intravenously treated patients.

Several studies have observed prolonged survival in patients without evidence of extrahepatic disease compared with those with such disease[4,15–17]. Despite the intention in our study to exclude patients with extrahepatic disease at trial entry, 36 per cent developed local recurrence or other metastases. Furthermore these recurrences occurred in all three treatment groups. These results are very similar to previously reported extrahepatic recurrence rates in treated patients who had apparently isolated liver metastases at initial presentation (37–43 per cent)[17–19].

In conclusion, HAE offers no apparent survival benefit in patients with unresectable colorectal liver metastases There was no significant advantage from HAI but the survival gain observed in all groups was greatest in the patients with initially low volume disease (<50 per cent hepatic replacement with tumour). Significant benefit is unlikely to be achieved without greater selection of patients in order to exclude more effectively patients with extrahepatic disease, and select those with less extensive intrahepatic disease. Although this will reduce the numbers of patients offered active treatment, a carefully selected subgroup may yet obtain useful survival gain. There is an urgent need for larger studies of selected patients to assess this possibility.

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Use of thermography in the differential diagnosis of phylloides tumour

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Thermography can be used as a method of diagnosing breast masses. We report our results of its use in the differential diagnosis of fibroadenoma from phylloides tumours ($n=47$ *and 20 respectively). Thermographic resolution (Th) and the difference in temperature between the tumour and a similar zone in the contralateral breast* (δ_2) *were compared. Thermograms were class Th1 (with a similar thermal pattern in both breasts without hypervascularization or hot points) and Th2 (with hypervascularization or a hot area with a thermal difference with the same area in the opposite breast* (δ_2) *of less than 2°C) in most (95·7 per cent) of the patients with fibroadenoma and were class Th5 (having one or more pathological sign) in 85 per cent of the patients with phylloides tumours. Patients with phylloides tumours had a mean* δ_2 *of 2·99°C whereas most of the patients with a fibroadenoma showed no difference in temperature. Their mean* δ_2 *was 0·2°C* ($P<0{\cdot}0005$)*. We conclude that thermography helps in differential diagnosis between a fibroadenoma and a phylloides tumour.*

Keywords: Thermography, phylloides tumour, fibroadenoma

Phylloides tumours of the breast are clinically benign but can recur locally and metastasize if sarcomatous[1,2]. Diagnosis is often only made on histology, since other methods such as mammography, sonography and fine needle aspiration are associated with a poor diagnostic discrimination[3–7]. Histologically, phylloides tumours are usually benign but some authors[2,8] describe local recurrence and metastases.

Although phylloides tumours and fibroadenomas have a similar fibroepithelial composition, phylloides tumours have a different stromal composition with greater mitotic activity. This difference in growth patterns probably correlates with increased metabolic activity and this, in turn, may be associated with different heat generation.

A prospective study was therefore undertaken examining thermography in the preoperative assessment of benign breast tumours evaluating thermographic differences between phylloides tumours and fibroadenomas.

Patients and methods

Between March 1980 and August 1989 a group of 10134 women were examined at the Breast Diseases Diagnostic Center of Concepción Mammography, thermography by liquid crystal plates and cytology by fine needle aspiration were carried out on all women in whom a breast mass was found. All patients with a histological diagnosis of phylloides tumour (20 patients) were compared with 47 women with a fibroadenoma selected taking all patients with this diagnosis during a period of 12 consecutive months

Thermograms were divided into five categories[9] characterized as· Th1, similar thermal pattern in both breasts without hypervascularization or hot points, Th2, presence of hypervascularization or a hot area with a thermal difference with the same area in the opposite breast (δ_2) of less than 2°C, Th3, existence of a hot area with a δ_2 from 2°C to 2·5°C or vascular asymmetry, Th4, appearance of widespread heat with δ_2 higher than 2°C or a single hot point with δ_2 higher than 2 5°C or disordered hypervascularization, Th5, presence of more than one of the preceding signs Grade Th1 was considered normal, grade Th2 corresponded to benign pathology, grade Th3 was suspicious and grades Th4 and Th5 were called 'exothermic' and considered as possibly malignant disease.

The patients were grouped according to their histological diagnosis, their thermographic grade and the δ_2 of any hyperthermic areas if they were present

Mean values were compared using a non-parametric Wilcoxon test for independent samples

Results

Relationship between thermographic and histological diagnosis

Thermography was normal or grade Th2 in most of the patients with fibroadenomas (*Figure 1*). In only two patients was an abnormal thermogram obtained. In patients with phylloides tumour thermograms were 'exothermic' in all but three cases (one Th1, one Th2 and one Th3). The patient with a Th2 thermogram had a benign phylloides tumour, according to a modified method of grading adopted by Norris and Taylor[10], but had local recurrence 28 months after initial conservative treatment and subsequently died with metastases.

Thermal differences between points of both breasts

In most patients with fibroadenoma no difference in temperature between breasts was demonstrated Only two patients had a small thermal difference ($\delta_2=0{\cdot}8$°C). Of the two patients with thermography class Th5, one had a δ_2 of 3 5°C and the other had δ_2 of 6·4°C. Patients with phylloides tumours had a mean δ_2 of 2·99°C and patients with fibroadenoma a

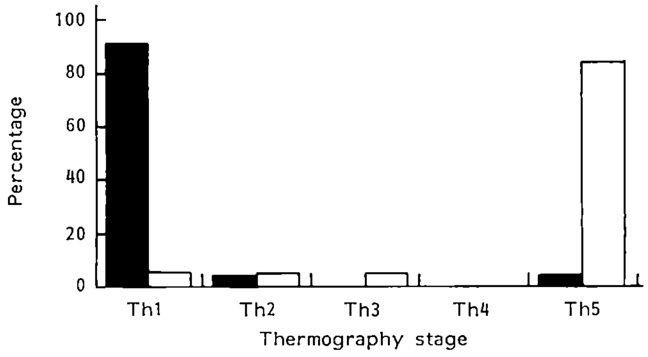

Figure 1 *Distribution of patients according to thermographic diagnosis* ■, *fibroadenomas,* □, *phylloides tumours*

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mean δ_2 of 0·24°C. This difference in δ_2 between patients with fibroadenoma and phylloides tumour was highly significant ($P < 0{\cdot}0005$).

Thermographic results were analysed for different types of phylloides tumours classified according to the method of Norris and Taylor[10]. Benign phylloides tumours had a smaller δ_2 than malignant and borderline tumours (2·5°C compared with 3·4°C) but this difference was not statistically significant.

Discussion

Considering the potential risk of local recurrence and metastasis in patients with phylloides tumour it is important to establish a preoperative diagnosis to allow definitive treatment at the first operation.

Clinical examination usually confuses a phylloides tumour with a fibroadenoma and mammography does not have the capacity to distinguish between the two. Ultrasound discriminates poorly between fibroadenomas, phylloides tumours and well-circumscribed malignancies even if the presence of elongated epithelial-lined, fluid-filled cystic spaces, characteristic of phylloides tumours[5], is present. Aspiration cytology has a high accuracy in the diagnosis of breast pathology but the phylloides tumour is usually confused with fibroadenoma, especially the juvenile or giant fibroadenoma, and with cancer, especially sarcomas[11].

Thermography is a non-specific method and, if used alone, has no special diagnostic value but, used in combination with other methods, it helps achieve a final diagnosis.

Both phylloides tumour and fibroadenoma present as circumscribed, solid and mobile masses, with well-defined limits on mammography and with fibroepithelial components on cytology. One significant difference is the high degree of cellular activity in phylloides tumours and this characteristic may be used for making a clinical differentiation. Thermography has the ability to demonstrate the increased heat generated by increased cellular activity. We have demonstrated that fibroadenomas are cooler than benign phylloides tumours and that these are cooler than malignant phylloides tumours.

Thermography is a useful aid in the preoperative diagnosis of phylloides tumour especially when used with other methods. The patient with a clinically and mammographically benign breast lesion which is 'hot' on thermography may be harbouring a phylloides tumour.

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CONTROVERSIES IN THE MANAGEMENT OF VENOUS DISORDERS

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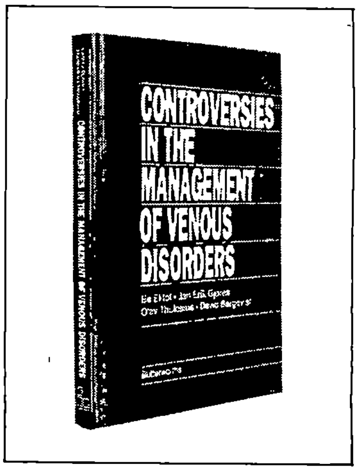

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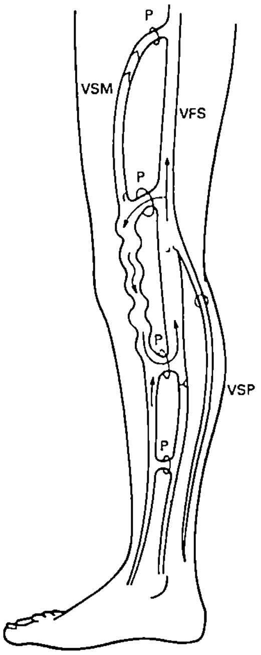
Controversies in the Management of Venous Disorders will be of particular interest to general surgeons, vascular surgeons, radiologists and physicians.



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Metabolic effects of recombinant human growth hormone: isotopic studies in the postabsorptive state and during total parenteral nutrition

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We have performed a series of isotopic studies in 25 adult patients with sepsis and/or trauma in order to determine the metabolic effects of recombinant human growth hormone (rHGH) administration. Twelve of the patients were receiving total parenteral nutrition, and 13 were eating a normal ward diet and were studied postabsorption. Energy and protein kinetics were quantified isotopically before rHGH administration and following a 3-day course of rHGH (20 units subcutaneously daily). In the total parenteral nutrition group the rate of net loss of protein decreased from 0·82(0·17) g kg^{-1} day^{-1} to 0·43(0·20) g kg^{-1} day^{-1} ($P<0.02$) following the administration of rHGH. The rate of appearance of leucine was not altered, suggesting that the improvement in nitrogen balance following rHGH was because of an increased rate of protein synthesis rather than reduced catabolism. In the postabsorptive group, rHGH treatment significantly increased the rate of appearance of free fatty acids (from 7·4(2·2) μmol kg^{-1} min^{-1} to 11·1(2·6) μmol kg^{-1} min^{-1}, $P<0.03$) and free fatty oxidation (from 1·3(0·4) μmol kg^{-1} min^{-1} to 1·7(0·4) μmol kg^{-1} min^{-1}, $P<0.06$), while the rate of leucine oxidation was reduced (from 0·44(0·05) μmol kg^{-1} min^{-1} to 0·26(0·03) μmol kg^{-1} min^{-1}, $P<0.005$). Glucose appearance and oxidation remained unchanged. These results suggest that fat was being oxidized in preference to protein, which resulted in a reduction in the net rate of loss of protein of 0·3 g kg^{-1} day^{-1} ($P<0.05$). We conclude that rHGH administration is capable of significantly reducing net protein loss in septic or injured surgical patients. Recombinant HGH may be clinically useful in supporting critically ill surgical patients who require intensive nutritional support.

Keywords: Human growth hormone, intravenous nutrition, protein catabolism, sepsis, trauma

Survival of critically ill surgical patients is increased by improvements in intensive care and optimizing the nutritional management of such patients is increasingly important Parenteral provision of excess calories and nitrogen does not compensate for the greatly accelerated rate of protein breakdown typical in such patients, and a state of net protein catabolism persists[1–3]. This leads to impairment of cardiopulmonary performance, immune function and wound healing[4] Improving the protein sparing efficacy of total parenteral nutrition in severely ill patients may therefore represent a significant clinical advance.

The effect of human growth hormone (HGH) on protein synthesis was first described more than 30 years ago[5]. Since 1985 recombinant human growth hormone (rHGH) has been available The effect of human growth hormone or its synthetic equivalent on protein metabolism has now been investigated in a number of studies of normal volunteers and patients on a variety of nutritional regimens[5–13]. Wilmore *et al.*, in the early 1970s, described an improved nitrogen balance in burn patients given HGH and an adequate dietary intake[7]. Subsequently they reported achieving protein anabolism by administering rHGH to normal volunteers[8] and depleted surgical patients[9] who were receiving hypocaloric intravenous feeding and were in negative nitrogen balance before rHGH treatment. Similar results have been described in normal volunteers given hypercaloric nutritional support[10], postoperative patients on hypocaloric intravenous feeding[11] and postoperative patients given no nitrogen and minimal caloric supplementation[12].

To date no study has examined whether the administration of rHGH is capable of reducing the rate of protein loss in patients with severe, acute illness receiving total parenteral nutrition. We have, therefore, studied the effects on protein metabolism of rHGH when administered to a group of severely ill septic or traumatized patients receiving total parenteral nutrition.

Little attention has been paid to the associated changes in fat and glucose metabolism. The effects of rHGH on energy metabolism have important implications for its protein anabolic properties and in the second part of this study we assessed the effect of rHGH on energy substrate turnover and oxidation in septic or injured patients who were sufficiently well to eat a normal diet.

Patients and methods

Isotopic studies were performed in 25 adult surgical patients in Auckland Hospital. Twelve of the patients were receiving intravenous nutrition and 13 were on a normal ward diet The patients were recovering from sepsis, trauma (musculoskeletal or major operation) or pancreatitis, conditions which have been previously demonstrated to be associated with an accelerated rate of net protein catabolism[1,14,15] Patients with evidence of diabetes mellitus or overt congestive heart failure or those receiving corticosteroids were excluded

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Table 1 *Patient details*

Group	Age	Sex	Weight (kg)	Sepsis score[16]	Diagnosis
Total parenteral nutrition controls	23	M	76	19	Multiple trauma, subphrenic abscess
	65	M	62	15	Duodenal perforation
	87	F	49	12	Pharyngeal perforation
	75	M	46	13	Postoperative, oesophagectomy
Total parenteral nutrition rHGH	58	F	73	12	Subphrenic abscess
	73	M	75	15	Anastomotic leak, pelvic abscess
	73	M	61	10	Postoperative oesophagectomy, pneumonia
	54	M	70	14	Caecal perforation, peritonitis
	62	M	65	14	Urinary peritonitis, post cystectomy
	58	M	82	21	Small bowel fistula, peritonitis
	66	F	57	11	Pancreatitis
	46	F	91	15	Pancreatitis, pneumonia
Postabsorptive patients					
Protein kinetics	51	M	122		Pancreatitis
	64	M	68		Haemopneumothorax, rib fractures
	67	F	49		Perforated duodenal ulcer
	72	M	67		Postoperative, aortic aneurysm repair
	69	M	77		Pancreatitis
Glucose kinetics	60	F	72		Postoperative, splenectomy
	65	F	48		Femur fracture
	23	M	72		Haemopneumothorax, rib fractures
	82	M	61		Femur fracture
Fat kinetics	57	F	67		Tibia and fibula fracture
	57	M	80		Dislocated knee
	32	M	92		Femur, patella fracture
	34	M	72		Tibia and fibula fracture

The study was approved by the institutional board of Auckland Hospital, and the use of radioisotopes was approved by the National Radiation Laboratory (New Zealand). Informed consent was obtained in all instances.

Patients

The clinical details of the patients are summarized in *Table 1* The 12 intravenously fed patients had been established on parenteral nutrition for a minimum of 3 days before a baseline study was performed, and were clinically stable over the time course of the study The mean age, weight, sex distribution and sepsis severity scores[16] did not differ significantly between the treatment and control (no treatment) groups. The studies of the patients on a normal ward diet were begun at between day 3 and day 12 after admission All patients completed the study protocol.

The intravenous nutrition solutions prescribed provided approximately 40 kcal kg^{-1} day^{-1} of non-protein calories The energy substrate requirement was administered as a calorically equal mixture of 50 per cent dextrose and 20 per cent lipid solutions (Intralipid®, KabiVitrum Laboratories, Stockholm, Sweden) An amino acid solution (Synthamin 17®, Travenol Laboratories, New South Wales, Australia) provided approximately 300 mg kg^{-1} of nitrogen daily, and vitamins (MVI 12, Armour Pharmaceuticals, Illinois, USA) and trace elements were added to the total parenteral nutrition bag A weekly dose of vitamin K (10 mg intramuscularly) was given routinely.

Study design

Total parenteral nutrition studies The baseline protein and energy metabolism of the 12 patients on total parenteral nutrition was measured on the first day of the study. This consisted of a primed constant infusion of isotopically-labelled metabolic tracers over a 3 h period and the performance of indirect calorimetry (*Figure 1a*)

Three of the rHGH-treated patients and all of the control patients received [^{14}C]-urea and 6[^{3}H]-glucose infusions in a manner which has been described elsewhere[15] The isotopic infusions enabled measurement of the rates of appearance of urea and glucose, and the rate of net protein loss was calculated from the rate of appearance of urea (Equation 1). For studies in four of the rHGH-treated patients, [^{15}N]-urea was substituted for [^{14}C]-urea In five of the rHGH-treated patients the rate of appearance of leucine into the plasma was determined by infusions of [^{14}C]-leucine. The leucine rate of appearance was assumed to be representative of total amino acid flux, and hence to provide an indication of the rate of whole body protein catabolism[17] The patients were then administered either 20 units subcutaneously of rHGH (Genotropin®, KabiVitrum Laboratories) at 08 00 hours for 3 days, or given no treatment (control group). The patients were restudied 24 h after the final injection of rHGH or the end of the control period with isotopic tracers and indirect calorimetry, allowing time for an insulin-like growth factor (IGF-1) response to occur after the final injection

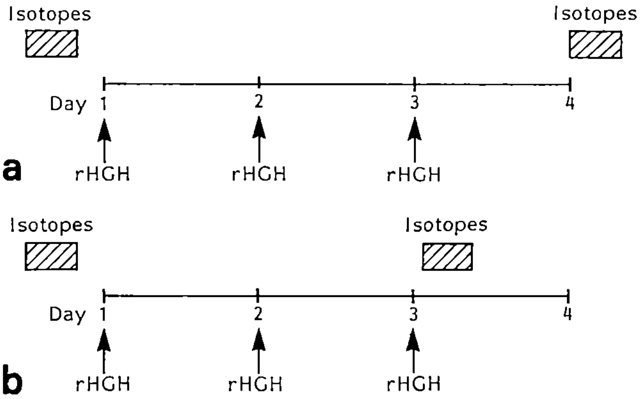

Figure 1 *Outline of the experimental protocols* **a** *Total parenteral nutrition patients*, **b** *postabsorptive patients*

Postabsorptive studies A similar protocol was followed in those patients on a normal ward diet (*Figure 1b*) in the postabsorptive state (at least 12 h postprandial) Following a baseline metabolic study with isotopic tracers and indirect calorimetry, the patients were administered three daily doses of rHGH in the manner described above. At 09 00 hours, 1 h after the final injection of rHGH, a second isotopic infusion was begun This was completed at 12.00 hours, so that the plasma specimens were collected 4 h after the final injection of rHGH. Indirect calorimetry was also repeated during this study period The peak plasma levels of rHGH occur 3–6 h after subcutaneous injection[18], and the time of isotopic infusion was chosen to coincide with this.

Glucose production and recycling were quantified in four patients with infusions of [^{14}C], 6[^{3}H] and 2[^{3}H]-glucose[19,20], and the rate of lipolysis and triglyceride recycling were determined by [^{14}C]-palmitate and [^{3}H]-glycerol infusions in four patients (Equation 3). The

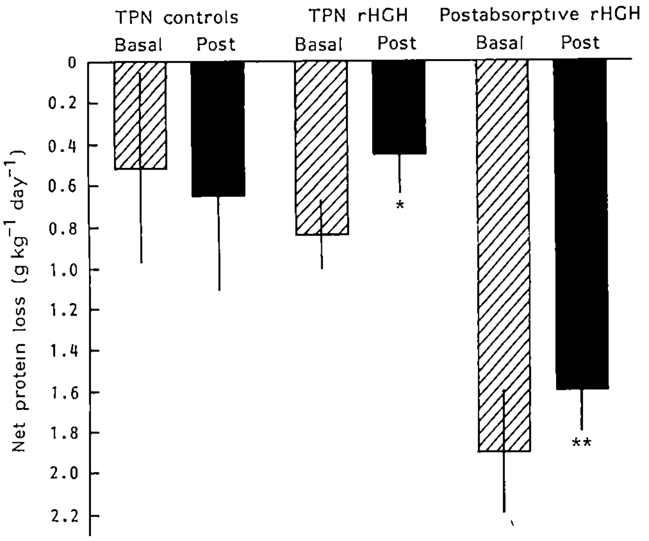

Figure 2 *The rate of net protein loss in total parenteral nutrition (TPN) and postabsorptive patients.* $^{*}P<0{\cdot}02$, $^{**}P<0{\cdot}05$

remaining five patients received [^{14}C]-leucine, and in addition [^{15}N]-urea was simultaneously infused in eight patients to determine the effect of rHGH on the rate of appearance of urea and hence on net protein loss

In order to determine the rates of glucose, free fatty acid and leucine oxidation, the bicarbonate pool was primed in each of the patients with an appropriate dose of NaH^{14}CO$_3$, and one mole samples of expired ^{14}CO$_2$ specimens were collected at the end of the isotopic infusions in a methylbenzonium/ethanol solution, and ^{14}CO$_2$ specific activity measured in a manner described previously[15,21] The rate of substrate oxidation was calculated using Equation 2. Frayn's equation was used to derive the rate of total fat oxidation from indirect calorimetry and urea turnover data[22]

Isotopic infusions The rate of appearance of urea was determined either by a 3 h infusion of [^{14}C]-urea (rate 1·5 nCi kg^{-1} min^{-1} and priming dose of 450·1), or when other [^{14}C]-labelled tracers were used, [^{15}N]-urea (rate 10 μg kg^{-1} min^{-1} and 450.1 prime)[23,24] Leucine kinetics were quantified by a 3 h infusion of [^{14}C]-leucine at a rate of 3 nCi kg^{-1} min^{-1} following a 60·1 leucine prime[24]. It has been previously demonstrated that with such an infusion isotopic equilibrium is reached within 2 h and remains stable for at least the next 2 h[25]

The rate of glucose production and recycling were determined with 3 h infusions 2 [^{3}H], 6 [^{3}H] and [^{14}C]-glucose at doses of 2 nCi kg^{-1} min^{-1} for the ^{3}H isotopes and 1 nCi kg^{-1} min^{-1} for [^{14}C]-glucose, following 80·1 primes[24]

Free fatty acid kinetics were quantified with 3 h infusions of 2 [^{3}H]-labelled glycerol (at 2 nCi kg^{-1} min^{-1} and 10·1 prime) and 1 [^{14}C]-palmitate bound to albumin (at 1 nCi kg^{-1} min^{-1} and without prime)[24]

The radioisotopes were obtained from Amersham International Laboratories (Amersham, Buckinghamshire, UK) and the [^{15}N]-urea from Tracer Technologies (Somerville, New Jersey, USA).

Indirect calorimetry. Indirect calorimetry was performed using a hood calorimeter with associated Sybron Taylor oxygen analyser (Hoddeson, UK) and ADC CO$_2$ analyser (Hertfordshire, UK) Following a period of accustomization to the hood, a reading was taken over a 20-min period during the last hour of the isotopic infusion

Sample analysis Blood samples were immediately chilled and separated. One millilitre samples were later used for the determination of plasma specific activity or enrichment. The methods for determination of [^{14}C] and [^{15}N]-urea have been described previously[15] The high pressure liquid chromatography method of Nissen *et al* [26] was modified and used to determine leucine concentration. The specific activities of 2[^{3}H] and 6[^{3}H]-glucose were determined by the method of Issekutz[20], whereby the ^{3}H from the two carbon of glucose is specifically cleaved by incubation with hexokinase and phosphoglucose isomerase (both supplied by Sigma Chemical Co, St. Louis, Missouri, USA) Palmitate concentration was quantified using a gas chromatography technique[24], and glycerol concentration by the method described by Galletti[27]

Plasma growth hormone levels were determined by an in-house double antibody radioimmunoassay (RIA) and calibrated against World Health Organisation standard 66/217. Plasma insulin was measured using an in-house double antibody RIA, and a human insulin standard provided by Wellcome New Zealand Ltd. (Otahuhu, Auckland, New Zealand, catalogue number RD 13) Plasma IGF-1 levels were determined using a double antibody RIA with the first antibody being rabbit anti-IGF-1 This method was standardized against human recombinant IGF-1 (Pitman Moore, Illinois, USA) The plasma levels of cortisol were measured using the Amerlex RIA Kit (Amersham International Laboratories)

Calculations. The rates of appearance of urea, leucine, glucose, glycerol and palmitate were calculated using either the Steele equation or a modification of the Steele equation applicable to stable isotopic tracers[24,28] The rate at which leucine in the total parenteral nutrition solution was being infused was subtracted from the determined rate of appearance of leucine to derive the endogenous rate of appearance of leucine The rate of net protein loss was derived as follows[24,29]

$$\begin{aligned}&\text{Net protein loss}=\text{protein intake}-(\text{rate of appearance of urea}\\&\quad\times 2\,\mu\text{mol N}/\mu\text{mol urea}\times 14\,\mu\text{g N}/\mu\text{mol N}\times 6{\cdot}25\,\mu\text{g protein}/\mu\text{gN}\\&\quad-1\,000\,000\,\text{g}/\mu\text{g}\times 60\,\text{min/h}\times 24\,\text{h/day})\end{aligned}\qquad(1)$$

The rate of substrate oxidation in the postabsorptive studies was calculated from the rate of oxidation of [^{14}C]-labelled tracer and resultant ^{14}CO$_2$-specific activity in expired breath[15].

$$\text{Oxidation rate}=\frac{SA_{^{14}\mathrm{CO}_2}\times V_{\mathrm{CO}_2}}{SA\,\text{substrate}\times k}\qquad(2)$$

where $SA_{^{14}\mathrm{CO}_2}$ = specific activity of ^{14}CO$_2$ in expired breath (dpm/μmol), V_{CO_2} = minute volume CO$_2$ (μmol kg^{-1} min^{-1}) and k = bicarbonate recovery correction factor[15]

Isotopic data were used to quantify the effect of rHGH on the activity of substrate cycles Such cycles exist when the forward and reverse reactions of a metabolic pathway, catalysed by different enzymes, are active simultaneously[30]. The extent of glucose recycling can be determined using specifically-labelled glucose tracers If a ^{3}H attached to a specific carbon is irreversibly cleaved by passing through one such cycle, then the activity of this cycle can be quantified by measuring the rate at which counts are lost[31] In this way, the activity of the glycolytic/gluconeogenic cycle is given by the difference between the rate of appearance of glucose determined by the 2 [^{3}H] and 6 [^{3}H] glucose tracers[20], and the rate of Cori cycling is given by the difference in rate of appearance between 6[^{3}H]-glucose and [^{14}C]-glucose[19].

Intracellular triglyceride cycling occurs when the hydrolysis of triglyceride into glycerol and free fatty acids and their re-esterification into triglyceride occur simultaneously within the adipocyte[32]. The rate of intracellular triglyceride cycling is given by the equation.

$$\begin{aligned}&\text{Intracellular cycling}=3(\text{rate of appearance of glycerol})\\&\quad-\text{rate of appearance of free fatty acids}\end{aligned}\qquad(3)$$

Statistical analysis Student's paired *t* test was used to determine the significance of changes between the pre and post rHGH results, and unpaired *t* tests were used to determine intergroup differences Results are expressed as mean(s.e m)

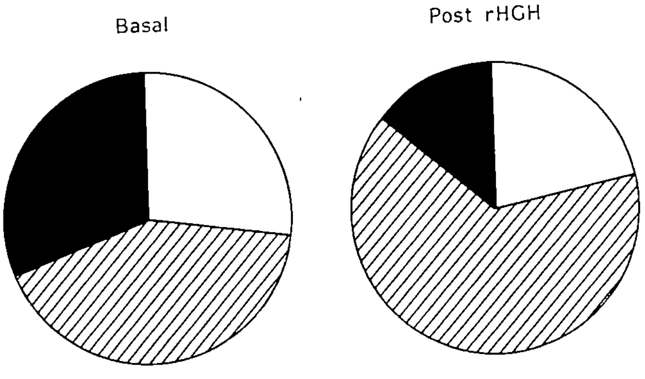

Figure 3 *Energy substrate oxidation in the basal state and following rHGH administration in postabsorptive patients* ■, *Protein,* □, *carbohydrate,* ▨, *fat. Glucose and protein oxidation were derived from the rate of oxidation of* [^{14}C]*glucose and leucine tracers and total fat oxidation from Frayn's equation*[22]. *The energy released per gram of substrate oxidized was calculated using the following data*[36] *glucose, 4·1 kcal g*$^{-1}$; *fat, 9·3 kcal kg*$^{-1}$ *and protein, 5·3 kcal kg*$^{-1}$

Results

Total parenteral nutrition patients

Hormones. Post-treatment plasma samples were collected from the patients receiving total parenteral nutrition 24 h after the final injection of rHGH and no increase in plasma growth hormone levels from basal values was seen in these patients, reflecting the short (17 min) half-life[33] of human growth hormone (*Table 2*). The plasma level of IGF-1 was more than doubled following the rHGH treatment and there was an increase of similar magnitude in the plasma levels of insulin. No change was observed in the plasma concentration of cortisol in the treatment or control groups.

Protein metabolism. There was a significant reduction in the rate of appearance of urea following rHGH administration from 9·7(1·0) μmol kg^{-1} min^{-1} to 7·5(0·8) μmol kg^{-1} min^{-1} ($P<0\cdot02$). When these data were converted to g protein kg^{-1} day^{-1} and the infused protein accounted for, this reduction in the rate of appearance of urea represented almost a halving of the net rate of protein loss (from 0·82(0·17) g kg^{-1} day^{-1} to 0·43(0·20) g kg^{-1} day^{-1}, $P<0\cdot02$). The rate of net protein loss in the control group did not change between the two study periods (0·51(0·46) g kg^{-1} day^{-1} basal and 0·66(0·43) g kg^{-1} day^{-1} after administration. The endogenous rate of appearance of leucine was unchanged following the rHGH course (4·4(1·1) μmol kg^{-1} min^{-1} basal and 4·4(0·8) μmol kg^{-1} min^{-1} after administration of rHGH) (*Figure 2*).

Table 2 *Plasma hormone levels*

Group	Basal	Post	Significance
Total parenteral nutrition controls			
HGH (μg/l)	3·2(1·2)	4·5(2·8)	n.s
IGF-1 (μg/l)	484(75)	502(115)	n.s
Cortisol (nmol/l)	477(65)	313(49)	n.s
Insulin (milliunits/l)	36(22)	28(15)	n.s
Total parenteral nutrition rHGH			
HGH (μg/l)	1·4(0·01)	1·6(0·3)	n.s.
IGF-1 (μg/l)	434(61)	1001(102)	$P<0\cdot0003$
Cortisol (nmol/l)	320(65)	435(61)	n.s.
Insulin (milliunits/l)	57(11)	120(30)	$P<0\cdot03$
Postabsorptive patients			
HGH (μg/l)	1·4(0·3)	39·9(5·6)	$P<0\cdot0002$
IGF-1 (μg/l)	271(32)	789(106)	$P<0\cdot003$
Cortisol (nmol/l)	422(36)	365(30)	n.s
Insulin (milliunits/l)	9(1)	25(5)	$P<0\cdot002$

Glucose and fat metabolism. Following rHGH administration there was a significant increase in the plasma glucose concentration (7·0(0·3) mmol l^{-1} to 8·3(0·7) mmol l^{-1}, $P<0\cdot03$) and an increase in the rate of endogenous glucose production (10·0(2·6) μmol kg^{-1} min^{-1} to 15·9(4·4) μmol kg^{-1} min^{-1}, $P<0\cdot07$). No change was seen in the rate of plasma glucose clearance. There were no significant changes in measurements of glucose concentration or kinetics in the control group.

Free fatty acid and glycerol kinetics were not determined in the patients receiving total parenteral nutrition. However, neither the plasma concentration of free fatty acids (0·58(0·11) mmol l^{-1} basal and 0·57(0·11) mmol l^{-1} after rHGH administration) nor glycerol (0·14(0·02) mmol l^{-1} basal and 0·12(0·02) mmol l^{-1} after rHGH administration) were altered in the rHGH treated group.

Indirect calorimetry. There was no change in the respiratory quotient following rHGH administration (0·94(0·01) basal and 0·93(0·02) after rHGH administration) nor was the rate of resting energy expenditure altered (1590(90) kcal day^{-1} basal and 1600(110) kcal day^{-1} after rHGH administration).

Postabsorptive patients

Hormones. At the time of sampling during the second study, 4 h after the final rHGH injection, the plasma growth hormone levels were almost 30-fold higher than basal in the postabsorptive group (*Table 2*), and both the plasma IGF-1 and insulin levels were increased nearly threefold The plasma cortisol levels were unchanged.

Protein kinetics. Following rHGH administration there was a consistent reduction in rate of appearance of urea (7·6(1·1) μmol kg^{-1} min^{-1} basal to 6·6(0·9) μmol kg^{-1} min^{-1} after rHGH administration, $P<0\cdot05$), which equated to a decrease in the rate of net protein loss from 1·91(0·27) g kg^{-1} day^{-1} to 1·66(0·23) g kg^{-1} day^{-1} ($P<0\cdot05$), and there were similar decreases in both the rate of appearance of leucine (3·7(0·6) μmol kg^{-1} min^{-1} basal to 2·7(0·5) μmol kg^{-1} min^{-1} after rHGH administration, $P<0\cdot04$) and rate of leucine oxidation (0·44(0·05) μmol kg^{-1} min^{-1} basal to 0·26(0·03) μmol kg^{-1} min^{-1} after rHGH administration, $P<0\cdot005$) (see *Table 3* and *Figure 2*).

Glucose metabolism. There were no significant changes in the glucose concentration, rate of glucose clearance or rate of oxidation following the rHGH treatment course. The rate of appearance of glucose and recycling data are presented in *Table 4*.

Table 3 *Response net protein loss to rHGH individual data*

Group	Sex and sepsis score								Mean(s.e.m.)
	M19	M15	M12	M13					
Total parenteral nutrition controls									
Basal	−0·54	0·68	1·67	0·23					0·51(0·46)
Post	−0·32	1·03	1·62	0·29					0·66(0·43)
	F12	M15	M10	M14	M21	F11	F15		
Total parenteral nutrition rHGH									
Basal	0·030	0·49	0·65	1·14	1·30	0·47	1·41		0·82(0·17)
Post rHGH	0·13	0·42	0·16	0·81	1·05	−0·44	0·89		0·43(0·20)*
	M	M	F	M	F	M	F	M	
Postabsorptive rHGH									
Basal	3·43	2·42	0·86	1·64	1·86	1·46	1·56	2·09	1·92(0·27)
Basal rHGH	2·65	2·09	0·78	1·54	1·84	1·00	1·13	2·24	1·66(0·23)‡

* $P<0\cdot02$, ‡ $P<0\cdot05$; negative data imply positive nitrogen balance. Sepsis score from Elebute and Stoner[16]

Table 4 *Glucose metabolism in postabsorptive patients*

	Basal	Post	Significance
Ra 6* (μmol kg^{-1} min^{-1})	15·9(1·6)	16·1(1·3)	n.s
Ra 2* (μmol kg^{-1} min^{-1})	17·9(2·1)	15·9(2·3)	n.s.
Ra 14* (μmol kg^{-1} min^{-1})	9·7(1·0)	9·9(0·8)	n.s.
Ra 2–Ra 6 (μmol kg^{-1} min^{-1})	3·2(1·0)	2·1(2·0)	n.s
Ra 6–Ra 14 (μmol kg^{-1} min^{-1})	3·7(1·0)	5·4(1·2)	n.s

*Rate of appearance (Ra) of glucose determined by simultaneous infusions of 6 and 2[^{3}H] and [^{14}C]-glucose tracers

Fat metabolism. The rate of appearance of free fatty acids in the plasma increased significantly from 7·4(2·2) μmol kg^{-1} min^{-1} to 11·1(2·6) μmol kg^{-1} min^{-1} ($P<0·03$) in the postabsorptive patients following rHGH treatment. This was not attended by an increase in the rate of appearance of glycerol of the same magnitude (3·3(0·7) μmol kg^{-1} min^{-1} to 3·7(0·8) μmol kg^{-1} min^{-1}, n.s.). The disparity in these changes was reflected in a decrease in the mean percentage of intracellular triglyceride recycling from 25 per cent to 1 per cent. The rate of oxidation of free fatty acids increased following rHGH administration in the postabsorptive patients (from 1·3(0·4) μmol kg^{-1} min^{-1} to 1·7(0·4) μmol kg^{-1} min^{-1}, $P<0·06$) (*Figure 3*).

Indirect calorimetry. The increase in free fatty acid oxidation seen in the postabsorptive patients following rHGH administration was associated with a significant reduction in respiratory quotient from 0·78(0·02) to 0·72(0·01) ($P<0·0005$). The rHGH course was not associated with a significant change in the resting metabolic expenditure (1560(150) kcal day^{-1} basal and 1580(120) kcal day^{-1} after rHGH administration).

Discussion

All but one of the total parenteral nutrition study patients was in a net negative nitrogen balance at the time of baseline study, reflecting the severity of the protein catabolic response to their illness. The rate of net loss of protein was nearly halved following rHGH administration, but in only one patient was a positive nitrogen balance achieved. This contrasts with the positive nitrogen balances achieved by rHGH treatment in the studies of Manson and Wilmore in normal volunteers[8] and in a group of depleted surgical patients[9], and of Ponting *et al.* in postoperative patients[11]. In these three studies the subjects received only about half their daily caloric requirement along with an adequate amount of nitrogen (between 100 and 200 mg kg^{-1} day^{-1}). The parenteral nutrition solution prescribed for our patients provided ample calories and 300 mg kg^{-1} day^{-1} of nitrogen. A positive nitrogen balance was not achieved, probably because the patients in our study were acutely and severely ill, not simply depleted or postoperative. The release of hormonal and inflammatory mediators accelerating the breakdown of protein was in excess of the potential of total parenteral nutrition and rHGH to promote nitrogen retention. None the less, rHGH had a significant protein-conserving effect in a group of patients whom we and others have shown to remain significantly catabolic despite optimal nutritional support[1–3]. Ziegler *et al.* have recently demonstrated that rHGH continues to promote protein anabolism in surgical patients when administered for periods as long as 25 days[9]. If the protein-sparing effect observed in the study group receiving total parenteral nutrition continued at the same rate for 2 weeks nearly 1·5 kg of wet muscle mass in a 70 kg patient would be conserved.

The reduction in net protein loss observed in the patients receiving total parenteral nutrition was not associated with a reduced rate of appearance of leucine. Assuming that the rate of leucine is representative of the rate of appearance of amino acids in general, then this result suggests that the administration of rHGH did not change the rate of whole body protein catabolism and implies that the improvement in nitrogen balance was a consequence of an enhanced rate of protein synthesis, a finding consistent with that of others[34].

As the antagonism of the actions of insulin seen after HGH administration is believed to be a property of the HGH molecule itself[35], in the second series of studies the second isotopic infusion was timed to coincide with maximal plasma HGH levels. Although neither the rate of appearance of glucose nor rate of oxidation were changed following rHGH treatment, free fatty acids were mobilized and oxidized at an accelerated rate. Both the rate of appearance of leucine and leucine oxidation were significantly reduced. We suggest that the reduction in leucine oxidation following rHGH administration was secondary to an increased reliance on fat oxidation for energy production. Presumably this protein-sparing effect would last until the fat stores were exhausted, which may not be long in a depleted patient with a high energy expenditure[10].

An increase in glycolytic/gluconeogenic cycling of some 70 per cent has been reported in acromegalic patients studied in the postabsorptive state[36], and we were interested to see whether rHGH would have a similar effect in surgical patients. However, no increase in the rate of glycolytic/gluconeogenic or Cori cycling was observed in the postabsorptive patients following rHGH administration in our study (*Table 4*). The effect on glucose recycling observed in acromegalics may be related to their chronic exposure to, in some cases, very highly elevated plasma HGH levels[37].

Our results suggest that rHGH administration influenced the rate of triglyceride recycling in the postabsorptive patients. Treatment with rHGH increased the rate of appearance of free fatty acids by two-thirds in this group, but did not significantly alter the rate of appearance of glycerol suggesting that the primary cause of the increase in the rate of appearance of free fatty acids was a reduction in re-esterification. Goodman obtained similar data in studies of laboratory animals[38], although others have reported parallel increases in glycerol release[39]. Although results from the two parts of our study were not directly comparable because of the different timing of the second study in relationship to the final rHGH injection, no increase in free fatty acids or glycerol concentration was seen in the patients on total parenteral nutrition. This may simply be a reflection of the plasma HGH levels not being raised at the time of the second study in these patients, as the lipolytic effects of HGH are believed to be a direct action of this hormone[35]. It has been reported by others that the lipolytic effect of HGH is effectively neutralized by parenteral feeding[9,10] or glucose alone[39].

Our study may be criticized because of the short term over which the isotopic measurements were made. It is very likely that the metabolic response to the rHGH injections varies over the time of absorption and catabolism of the exogenous hormone. Accordingly, the magnitude of the changes we have measured may not be consistent over a 24-h period. A prolonged infusion of rHGH to ensure a consistent response or a prolonged infusion of isotopic tracers associated with multiple sampling over time to measure differences in response following the final rHGH injection would circumvent this interpretational difficulty. These alternatives were not clinically feasible.

In summary, a short course of rHGH in severely ill surgical patients receiving total parenteral nutrition is capable of almost halving their rate of net protein loss. A mean positive nitrogen balance was not achieved. In the postabsorptive setting, the protein-sparing effect observed following rHGH administration appeared to result from the oxidation of fat in preference to protein. rHGH may have therapeutic potential in the nutritional management of septic or traumatized patients who require intensive support.

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Influence of glucagon on protein and leucine metabolism: a study in fasting man with induced insulin resistance

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The counter-regulatory hormones, including glucagon, may be involved in the generation of postoperative negative nitrogen balance. We examined the influence of glucagon on whole body and forearm muscle protein kinetics, determined by L-[*1-*^{13}*C,*^{15}*N*]*leucine, in two matched groups of healthy fasting subjects. In one study somatostatin alone was infused continuously* (*0·12 mg* h^{-1}) *and in another with glucagon* (*0·04 mg* h^{-1}) *to generate insulin resistance. Somatostatin infusion increased leucine oxidation* ($P < 0{\cdot}05$) *and reduced the negative protein balance* ($P < 0{\cdot}01$) *across the forearm; the 15 per cent decrease in protein breakdown was not significant. Whole body leucine kinetics showed increased flux* ($P < 0{\cdot}05$) *and synthesis* ($P < 0{\cdot}01$) *but reduced oxidation* ($P < 0{\cdot}05$). *Hyperglucagonaemia caused a threefold enhancement of leucine oxidation* ($P < 0{\cdot}02$), *while the negative protein balance further increased* ($P < 0{\cdot}05$) *across the forearm. Whole body leucine flux was unchanged; oxidation increased* ($P < 0{\cdot}01$) *and synthesis decreased* ($P < 0{\cdot}01$). *These studies confirm that physiological hyperglucagonaemia during insulin resistance is catabolic in the short-term and indicates, for the first time, that glucagon may influence muscle protein metabolism acutely in man. We suggest that therapeutic manoeuvres designed to reduce glucagon levels after surgery may ameliorate protein kinetic abnormalities.*

Keywords: Whole body, forearm, leucine kinetics, somatostatin, glucagon

The postoperative period is characterized by increased negative nitrogen balance[1] and the counter-regulatory hormone glucagon has been implicated in this process[2].

Glucagon infusion, often extended over several days, usually produces increased negative nitrogen balance[3–5] although not consistently so[6]. Amino acid balance across the forearm has been shown to be either unaffected[7] or to become positive[5] with physiological increments of glucagon. Few studies have used metabolic tracers to evaluate directly the effect of glucagonaemia on protein metabolism. One report noted no effect on whole body leucine kinetics during chronic infusion of four counter-regulatory hormones (including glucagon) over 3 days in obese individuals[8]. We have recently shown that acute hyperglucagonaemia significantly increases whole body leucine flux, proteolysis and oxidation in man[9] Ostaszewski and Nissen[10], however, using the immature pig, showed that in the fasted state hyperglucagonaemia failed to influence proteolysis

We have published data on leucine kinetics across the forearm in fasting and fed normal subjects using doubly-labelled L-[1-^{13}C,^{15}N]leucine[11,12]. The purpose of this study was to evaluate the influence of hyperglucagonaemia on leucine metabolism and to determine the acute effect on whole body and muscle protein kinetics. After surgery the negative nitrogen state is frequently associated with insulin resistance which we attempted to mimic by use of the naturally occurring peptide somatostatin, somatotrophic release inhibitory factor (SRIF).

Patients and methods

Materials

L-[1-^{13}C,^{15}N]leucine (^{13}C,^{15}N, 99 atom per cent) was obtained from Tracer Technologies (Newton, Massachusetts, USA) and sodium bicarbonate (^{13}C, 99 atom per cent) from Cambridge Isotope Laboratories (Woburn, Massachusetts, USA). These isotope solutions were prepared under sterile conditions in pyrogen-free normal saline

Somatostatin was purchased from Serono Laboratories (UK) Ltd (Welwyn Garden City, UK) and glucagon from Novo Laboratories Ltd. (Basingstoke, UK).

Subjects

The clinical details of the subjects studied for somatostatin infusion alone were (figures are mean(standard deviation)) 6 men, 1 woman; age 31 5(1·6) years, weight 69 4(8 2) kg; body mass index 22 8(2·3), and for somatostatin plus glucagon infusion· 6 men, 1 woman, age 33·4(10 7) years; weight 71 3(8·3) kg, body mass index 22 4(2·3) Three subjects took part in both studies. All were in excellent general health with no significant previous illnesses or positive family history of diabetes mellitus. All were consuming a weight-maintaining diet and were taking no medication at the time of the study or during the preceding month One subject in each group smoked cigarettes.

The protocols were approved by the Ethical Committee at Northwick Park Hospital and all individuals gave informed consent following a full explanation of the study protocol.

Protocol

Each subject arrived in the metabolic unit of the Clinical Research Centre at 08.00 hours following a 12–14 h overnight fast Three intravenous catheters were inserted, the first into a deep vein and its suitability confirmed ($HbO_2 < 55$ per cent) The other two were placed in superficial veins of the contralateral arm· one in the upper arm for tracer infusion, the other into a vein on the dorsum of the hand for arterialization by the hot box technique ($HbO_2 > 90$ per cent)[13]. The superficial circulation of the hand was excluded by inflating a paediatric sphygmomanometer cuff around the wrist to 200–220 mmHg for 2 min before deep vein sample collection After simultaneous collection of basal arterialized and deep vein bloods prime injections of L-[1-^{13}C,^{15}N]leucine (0 9 mg kg^{-1}) and $NaH^{13}CO_3$ (0 18 mg kg^{-1}) were given followed by a continuous infusion of L-[1-^{13}C,^{15}N]leucine (1 0 mg kg^{-1} h^{-1}). After 2 h four sets of arterialized and deep vein bloods were taken sequentially over a 40-min period.

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Table 1 *Effect of infusion of somatostatin (SRIF) and SRIF with glucagon on biochemical variables and whole body leucine kinetics in healthy fasting individuals*

	Basal	SRIF infusion alone ($n=7$)	Basal	SRIF + glucagon ($n=7$)
Arterialized blood glucose (mmol l^{-1})	4·8(0·3)	4·3(0·9)	4·6(0·2)*	9·6(1·6)
Plasma insulin (microunits ml^{-1})	10(5)‡	6(2)	8(4)‡	14(8)
Plasma glucagon (pg ml^{-1})	183(68)‡	113(44)	157(40)*	750(390)
O_2 uptake (ml min^{-1})	250(34)	244(43)	281(52)	292(54)
CO_2 production (ml min^{-1})	193(24)	183(24)	211(35)	209(36)
Whole body leucine flux (μmol kg^{-1} h^{-1})	81(11)‡	86(9)	93(9)	91(10)
Oxidation, (μmol kg^{-1} h^{-1})	16(3)*	14(3)	15(2)‡	18(2)
Synthesis (μmol kg^{-1} h^{-1})	65(8)†	72(7)	78(8)†	73(9)

Values are mean(s.d.) *P* value obtained using paired *t* test. * $P<0·001$, † $P<0·01$, ‡ $P<0·05$

Table 2 *Leucine and muscle protein metabolism across the resting forearm during infusion of somatostatin (SRIF) alone or with glucagon*

	SRIF alone ($n=7$)		SRIF + glucagon ($n=7$)	
	Basal	SRIF	Basal	SRIF + glucagon
Oxidation	5·1(2·5)‡	9·8(5·4)	6·7(4·1)†	19·6(7·8)
Breakdown	116·6(20·5)	99·0(28·1)	97·0(28·9)	113·5(16·7)
Synthesis	71·1(14·1)	73·0(13·6)	61·5(11·5)	52·3(23·3)
Net balance	−45·3(11·3)*	−27·3(20·1)	−35·0(18·9)‡	−61·2(15·3)
Deamination (T_1)	207·2(60·4)	225·1(89·2)	231·4(119·1)‡	299·2(169·1)
Reamination (T_2)	194·0(59·8)	215·1(89·3)	218·6(118·7)	275·0(178·9)
T_1.T_2 ratio	1·07(0·02)	1·05(0·03)	1·07((0·03)	1·13(0·08)
C-flux	121·8(31·3)	100·9(32·5)	104·7(28·1)	116·4(18·3)
N-flux	310·6(72·6)	314·0(110·7)	315·6(129·9)	388·5(191·3)
MPSR	0·055(0·01)	0·056(0·01)	0·048(0·01)	0·040(0·02)

All units are nmol 100 ml^{-1} per min except muscle protein synthetic rate (MPSR) which is per cent per h. Values are mean(s.d.) *P* value obtained using paired *t* test * $P<0·01$, † $P<0·02$; ‡ $P<0·05$

Following these samples somatostatin (0·12 mg h^{-1}), with or without glucagon (0·04 mg h^{-1}) was given and an additional four sets of arterialized and deep vein blood samples taken after a further 2 h of tracer infusion, again over some 40 min.

Forearm blood flow was measured by mercury strain-gauge plethysmography[14] immediately before and after blood sampling. At least four separate measurements were taken to calculate the mean blood flow. For the entire study period the subject lay quietly on a bed to ensure the measurements were those from the resting forearm. Indirect calorimetry was recorded continuously during the study using a ventilated hood technique[15].

Model

The forearm model requires the measurement of net arteriovenous balance of both labelled essential amino acid tracer and unlabelled tracee across the muscle bed. Employing a constant infusion of [1-^{13}C,^{15}N]leucine and measuring the resultant leucine, ketoisocaproic acid (KIC) and CO_2 concentrations (together with the enrichment of [1-^{13}C,^{15}N]leucine, [^{15}N]leucine, [1-^{13}C]leucine, [1-^{13}C]KIC and $^{13}CO_2$) and blood flow permit the required simultaneous balance equations to be solved[11,12]. Whole body protein kinetics are calculated from the tracer infusion rate and the level of tracer enrichment observed in the plasma under steady state conditions[6,10]. The calculated tracer flux can then be partitioned into synthesis and oxidation, the latter being the product of $^{13}CO_2$ enrichment in expired air and the total CO_2 production rate. Plasma [^{13}C]leucine enrichment was used to represent the precursor pool for whole body leucine flux and plasma [^{13}C]ketoisocaproic acid enrichment, leucine oxidation.

Analytical methods

All blood was centrifuged immediately at 4°C and plasma separated and stored at −70°C until analysis. Blood for glucose estimation was collected into fluoride/oxalate tubes and measured by a standard hexokinase method within 48 h.

Specimens for glucagon were transferred to tubes containing 0·1 ml 20 000 kallikrein inactivator units aprotinin (Bayer UK Limited, Newbury, UK). The hormone was measured using the Novo radioimmunoassay kit (Novo Research Institute, Copenhagen, Denmark). Plasma insulin was measured by radioimmunoassay[16], all samples from each individual being analysed together.

Plasma leucine and its keto acid analogue α-ketoisocaproic acid (α-KIC) concentration and isotope enrichment were measured by selected-ion monitoring gas chromatography–mass spectrometry[17]. The concentration and isotopic enrichment of whole blood CO_2 and ^{13}C enrichment in expired breath was performed by isotope ratio mass spectrometry[18].

The paired *t*-test compared basal and subsequent results during hormonal manipulation. The steady state was considered to have been reached when the coefficient of variation (s.d./mean) of plasma leucine, α-KIC and CO_2 isotope enrichment and concentration was <10 per cent. This established criterion[19] was easily fulfilled in all studies reported.

Results

As demonstrated in *Table 1* somatostatin (SRIF) reduced plasma insulin ($P<0·01$) and glucagon ($P<0·01$) while combined SRIF–glucagon infusion increased blood glucose ($P<0·001$), plasma glucagon ($P<0·001$) and insulin ($P<0·01$). Both SRIF alone and SRIF–glucagon reduced the respiratory quotient (0·77(0·02) to 0·74(0·02), $P<0·01$ and 0·75(0·02) to 0·72(0·03), $P<0·01$ respectively). Whole body leucine flux (proteolysis) was increased ($P<0·05$), oxidation decreased ($P<0·05$) and synthesis increased ($P<0·01$) by SRIF alone. In contrast, SRIF–glucagon increased leucine oxidation ($P<0·02$) and reduced synthesis ($P<0·01$).

Across the forearm (*Table 2*) SRIF promoted leucine oxidation ($P<0·05$) and decreased net negative protein balance by 40 per cent ($P<0·01$) which appeared predominantly to reflect inhibited proteolysis. Both leucine ($P<0{\cdot}02$) and α-KIC ($P<0{\cdot}05$) balance were reduced while all other variables of leucine metabolism across the forearm remained essentially unchanged Combined SRIF–glucagon infusion promoted total forearm blood flow (2·7(0 6) compared with 3·9(0·8) ml 100 ml^{-1} min^{-1}; $P<0{\cdot}05$) and leucine oxidation ($P<0{\cdot}02$), increased net negative protein balance ($P<0\ 05$), and stimulated deamination of leucine to α-KIC ($P<0{\cdot}05$).

The possibility that hyperglucagonaemia stimulated oxidation of the higher naturally ^{13}C-enriched endogenous carbohydrate rather than representing increased oxidation of amino acid was investigated by infusing SRIF–glucagon with no L-[1-^{13}C,^{15}N]leucine for 3 hours in two post absorptive healthy males In these subjects expired breath $^{13}CO_2$ enrichment basally was 0·0091(0·0006), while it was 0·0092(0·0007) during SRIF–glucagon infusion. Blood glucose levels at these times were 5·0(0·6) and 9·2(2 1) mmol l^{-1}

Fractional muscle protein synthetic rate was calculated by assuming that the forearm muscle content was 72 per cent in men and 58 per cent in women[20], that the protein content of muscle was 18 per cent[21] and that the leucine content of protein was 8 per cent[22] Muscle protein synthetic rate before and during SRIF infusion alone was 0 05(0·01) and 0 06(0·01) per cent h^{-1} while during SRIF–glucagon infusion these respective values were 0·05(0·01) and 0·04(0·02) per cent h^{-1}

Discussion

These studies demonstrate that the effect of acute physiological hyperglucagonaemia on whole body and forearm muscle protein metabolism is catabolic and is further evidence that this counter-regulatory hormone may influence negative nitrogen balance after surgery

The overall metabolic response in the whole body and across muscle due to somatostatin (SRIF) was small, although the net negative protein balance was significantly reduced. It is likely that the early SRIF response results from specific inhibition of glucagon response[23]. This is indirect evidence that glucagon can influence protein kinetics acutely and confirmation was provided by infusing glucagon which promoted net negative protein balance both in the whole body and across forearm muscle.

The effects of hyperglucagonaemia have to be interpreted with caution. First, the infusion rate of SRIF during hyperglugonaemia was designed to create insulin resistance rather than completely inhibit its release. Thus, generation of insulin resistance with respect to carbohydrate metabolism may not have been obtained for amino acid kinetics. Given the evidence that, in man, insulin principally inhibits proteolysis[24–26] its elevation in the current study may account for our failure to demonstrate hyperglucagonaemic stimulation of whole body protein breakdown as noted when associated with reduced insulin concentrations[9]. Second, considerable intersubject variability of absolute values for leucine and muscle protein kinetics across the forearm were observed – a common feature of this technique[5,7,27]. Despite these large intersubject variations, reflected in the magnitude of the standard deviations, both basal studies yielded comparable mean values for all measured parameters; their differences being no greater than those of the whole body. All subjects responded in a broadly similar fashion to the SRIF or SRIF–glucagon infusion despite large intersubject differences The propagated errors, arising from the number and range of measurements, are substantial but the model appears capable of demonstrating physiological trends.

Hyperglucagonaemia increased, albeit not significantly, muscle protein breakdown and reduced synthesis, similar to responses in animals[28–30]. Leucine oxidation across the forearm was increased, particularly by hyperglucagonaemia The possibility that a change in substrate oxidation, from lipid to more naturally ^{13}C-enriched endogenous carbohydrate[31], rather than actual promotion of leucine oxidation was unlikely as infusion of SRIF and glucagon failed to change expired breath CO_2 enrichment. Increased leucine oxidation by glucagon has been noted in pigs[10] and in man[9] and is compatible with the suggestion that the hormone activates, by dephosphorylation, the branched chain α-keto acid dehydrogenase enzyme complex[32].

The forearm model permits calculation of fractional muscle protein synthesis rate, hitherto measured by the invasive muscle biopsy technique. The results generated in the basal portion of both studies were in close agreement with values recently reported using serial muscle biopsies[33,34], providing supportive evidence for their validity

In conclusion, this study confirms that hyperglucagonaemia is hypercatabolic with an acute influence on muscle protein metabolism. This response may be a mechanism whereby amino groups are provided as substrate for gluconeogenesis Despite the constraints of the forearm model used here the data it generates may enhance knowledge about the response to trauma. It may be of use to study protein kinetics after surgery

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Short note

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Role of thallium-201/technetium-99m subtraction scanning in persistent or recurrent hypercalcaemia following parathyroidectomy

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Surgery for primary hyperparathyroidism is successful in 90–95 per cent of cases[1,2]. The place of preoperative localization techniques is unclear, but their use is mandatory where reoperation for persistent or recurrent hyperparathyroidism is indicated[3]. A number of localization techniques are available and the performance of high resolution ultrasound, computed tomographic scanning, magnetic resonance imaging and selective venous catheterization before cervical re-exploration for hyperparathyroidism, has been investigated[4,5].

Thallium-201/technetium-99m subtraction scanning has high sensitivity when compared with operative findings at initial neck exploration[6]. The present study attempts to define the performance of this technique in the investigation of persistent or recurrent hypercalcaemia following parathyroidectomy.

Patients and methods

740 consecutive patients with hypercalcaemia or proven hyperparathyroidism have been investigated using thallium-201/technetium-99m subtraction scanning during a 6-year period (1983–89). Twenty-six of these patients, who were referred from a total of ten hospitals, had recurrent or persistent hypercalcaemia (serum calcium $>2{\cdot}75$ mmol/l on two occasions) following previous parathyroidectomy. Because of our referral pattern, only 15 of these patients had a firm biochemical diagnosis of hyperparathyroidism with detectable serum levels of parathyroid hormone. All 26 patients underwent isotope scintigraphy following the initial unsuccessful neck exploration and these scans have been retrospectively correlated with the presence, site and histology of any abnormality found at reoperation, or with the clinical outcome where reoperation was not undertaken

Parathyroid scintigraphy was performed according to the method described by Young *et al*[6] At reoperation a search for all residual parathyroid tissue was made, a biopsy was performed and subjected to frozen section examination Residual abnormalities were removed and submitted for frozen and paraffin section histology Weighing of specimens was not performed.

We have assumed that patients not undergoing repeat neck exploration who later became normocalcaemic had no residual parathyroid abnormality in the neck.

Results

Of the 26 patients, 17 had positive scans (*Figure 1*). Fourteen of

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Based on a presentation to the British Association of Endocrine Surgeons, Lille, France, May 1989

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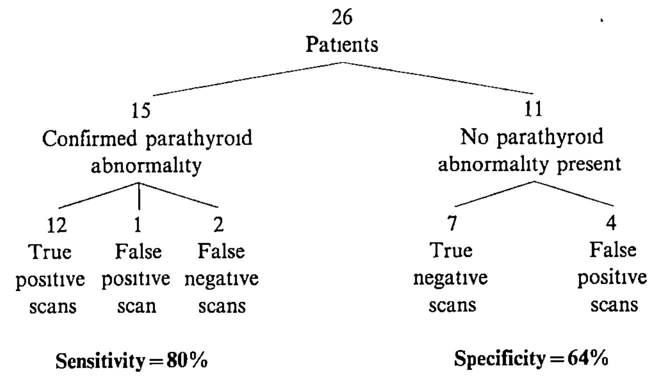

Figure 1 *Results of isotope scans in patients with recurrent/persistent hypercalcaemia*

these patients underwent repeat neck exploration and 13 had a detectable abnormality. Of these patients 11 had a single adenoma of which ten were accurately located. The adenoma not accurately located was designated a false positive result although it was shown in the correct side of the neck. One patient had two distinct adenomas. One recurrent parathyroid carcinoma was correctly located. Thus, there were 12 true positive scans. The patient in whom no abnormality was found at operation subsequently became normocalcaemic as did the three patients who were not re-explored. We have assumed that these four patients had no parathyroid abnormality and, therefore, had false positive scans.

Nine of the 26 patients had negative scans Three patients, who were in renal failure and initially presented with secondary hyperparathyroidism, were not re-explored and subsequently became normocalcaemic. Six patients underwent repeat neck exploration despite having negative scans. In four of these patients no abnormality was found, but they subsequently became normocalcaemic (seven true negative scans). Two patients, however, had a mediastinal adenoma and thus had false negative scans.

Thus, 12 of the 15 patients with abnormal glands had accurately localizing scans (sensitivity = 80 per cent). Seven of the 11 patients whose hypercalcaemia resolved (therefore they probably did not have hyperparathyroidism) had negative scans (specificity = 64 per cent).

Thirteen of the 17 positive scans and all 12 true positive scans were in patients with proven recurrent or persistent hyperparathyroidism. Seven of the nine negative scans (including all seven true negative scans) were in hypercalcaemic patients who did not have a firm diagnosis of recurrent or persistent hyperparathyroidism.

There were no complications of the investigation.

Discussion

Parathyroid imaging techniques, including scintigraphy, are conventionally used to locate abnormal glands where a diagnosis of hyperparathyroidism has been established. The nature of our referral pattern was such that 11 patients were scanned on the basis of hypercalcaemia rather than biochemically confirmed hyperparathyroidism This provides an opportunity to assess the diagnostic as well as the localization potential of isotope scintigraphy in recurrent or persistent hyperparathyroidism.

The high sensitivity achieved in this study (58 per cent) compares favourably with that of isotope scintigraphy in the investigation of *de novo* hyperparathyroidism[6] and with that of other localization modalities used in recurrent or persistent hyperparathyroidism[7]. The two false negative scans were obtained in patients with a mediastinal adenoma, a situation where myocardial isotope uptake is acknowledged to make parathyroid detection difficult[8]

In contrast, the relatively poor specificity of 64 per cent, with five false positive results, confirms the unsuitability of this technique for diagnostic use. All 15 patients with a biochemical diagnosis of recurrent or persistent hyperparathyroidism had a detectable parathyroid abnormality. In no patient without a biochemical diagnosis of hyperparathyroidism was an abnormality found. A firm biochemical diagnosis of recurrent or persistent hyperparathyroidism should be made in all patients before arranging isotope scintigraphy, which should be regarded primarily as a localization technique.

The cause of hypercalcaemia is unclear in the patients who spontaneously recovered. Four of these patients were in chronic renal failure and may have been taking inappropriately high doses of 1α-hydroxycholecalciferol, giving them spurious hypercalcaemia.

In conclusion, thallium-201/technetium-99m is a sensitive and safe localization technique which is of great value in the management of patients with proven recurrent or persistent hyperparathyroidism

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Elective abdominal surgery depresses muscle protein synthesis and increases subjective fatigue: effects lasting more than 30 days

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Ten patients without metabolic disease undergoing elective cholecystectomy were studied before surgery and on days 3, 10, 20 and 30 after operation. Percutaneous muscle biopsies were taken and protein synthesis was determined from the total concentration and size distribution of ribosomes. The subjective feeling of fatigue was estimated using a visual analogue scale. The nitrogen balance was calculated at 20 days following surgery. The mean(s.e.m.) total concentration of ribosomes per milligram of DNA decreased by 27·5(6·6) per cent ($P<0{\cdot}01$)*, 44·5(6·5) per cent* ($P<0{\cdot}001$)*, 48·3(8·9) per cent* ($P<0{\cdot}001$) *and 45·0(8·2) per cent* ($P<0{\cdot}01$) *on days 3, 10, 20 and 30, respectively. By 30 days after surgery no sign of restoration of normality was seen. The relative proportion of polyribosomes had decreased by 20·4(6·4) per cent* ($P<0{\cdot}05$) *on the third postoperative day and by 20·4(3·9) per cent* ($P<0{\cdot}01$) *on the tenth postoperative day and was restored to the preoperative level by day 20. The subjective fatigue score increased after operation and five of nine patients had not regained their preoperative scores 30 days after surgery. The daily nitrogen balance was negative for 5 days. The cumulated nitrogen losses were not restored until after 18 days following surgery. Elective abdominal surgery caused a sustained depression of protein synthesis for over 30 days, a longer period than previously presumed. These results show that long-term follow-up is required when the effect of different postoperative nutritional regimens are to be evaluated.*

Keywords: Surgery, protein synthesis, muscle biopsy, ribosomes, nitrogen balance, fatigue, muscle strength

The post-traumatic state is accompanied by a series of metabolic changes, the loss of body protein and negative nitrogen balance being the most characteristic[1–3] Skeletal muscle proteins are the major source of the excreted nitrogen[2]. After moderately severe trauma without septic complications the decrease in muscle protein synthesis, rather than an increase in the rate of degradation, is responsible for the loss of proteins in skeletal muscle[4–6]. The total concentration of ribosomes, as well as the relative proportion of polyribosomes, decreases on the third day following elective surgery, indicating a fall in protein synthesis in skeletal muscle[6]. It is not known when these changes reverse to the preoperative level Many patients complain of pronounced tiredness, sometimes for more then 1 month following abdominal surgery[7]. The aetiology of this 'postoperative fatigue syndrome' is poorly understood[7,8]. Muscle weakness is a frequent complaint following surgery and trauma, but no effective method has yet been found to assess this phenomenon objectively. It is also unclear whether the postoperative fatigue and muscle weakness have any biochemical correlate in skeletal muscle.

The aim of this study was to make a long-term investigation of the natural course of events after elective upper abdominal surgery with special emphasis on fatigue, muscle protein synthesis and whole body nitrogen balance.

Patients and methods

Patients

Patients ($n=10$) without metabolic disease scheduled for elective cholecystectomy participated in the study One patient dropped out of the study on the tenth postoperative day for social reasons and one patient did not participate in the muscle biopsy part of the study The characteristics of the patients and the operative procedure are shown in *Table 1*.

The patients were examined before operation, and in the morning after overnight fasting on days 3, 10, 20 and 30 after surgery Percutaneous muscle biopsy specimens were taken before surgery immediately after the induction of anaesthesia and under local anaesthesia on days 3, 10, 20 and 30 after the operation Five of the patients recorded their complete food intake and collected urine in 24-h aliquots for 20 days after surgery The operation took place the day after admission to the hospital after overnight fasting. All patients were operated on under general anaesthesia comprising thiopentone sodium, fentanyl, succamothon chloride, droperidol, pancuronium and O_2/N_2O On the day of operation the patients were given 3000 ml of an electrolyte solution (Na, 70 mmol/l, Cl, 45 mmol/l; acetate, 25 mmol/l) containing 2·5 per cent glucose (Rehydrex®, Pharmacia Infusion, Uppsala, Sweden) intravenously The oral intake started on the first postoperative day and was gradually increased at will. The

Table 1 *Characteristics of the patients and surgical procedure*

Men women	3 7
Age in years	51·6(4·4)
Weight in kg	67 2(5·2)
Height in cm	167 2(3 1)
Operating time in min	89 5(8 1)
Peroperative blood loss in ml	135(26)

Values are mean(s e m.)

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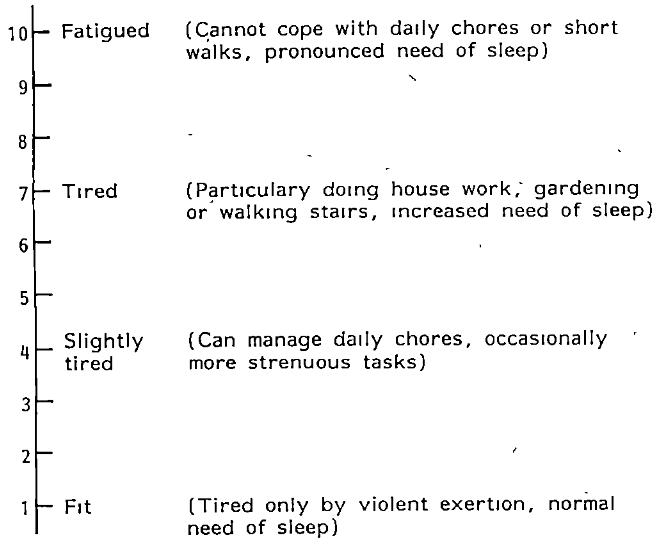
10 Fatigued (Cannot cope with daily chores or short walks, pronounced need of sleep)
9
8
7 Tired (Particulary doing house work, gardening or walking stairs, increased need of sleep)
6
5
4 Slightly tired (Can manage daily chores, occasionally more strenuous tasks)
3
2
1 Fit (Tired only by violent exertion, normal need of sleep)

Figure 1 *Fatigue scale used for quantitation of subjective feeling of fatigue in patients undergoing abdominal surgery From Christensen et al* [7]

patients were mobilized on the first day after surgery and received no prophylactic pharmacological treatment against thrombosis.

The nature and purpose of and the risks involved in the experimental procedure were explained to the patients before obtaining their voluntary consent. The research protocol was approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden.

Examination

A visual analogue scale was used to estimate the subjective feeling of fatigue[7]. At each examination the patients were presented with a constructed fatigue scale (*Figure 1*). The scale was thoroughly explained to the patients by the same investigator each time in a standardized manner. The scores were decided on by the patient himself at leisure, without any information about previous results. The patients were weighed on the same scale at each examination, wearing only their underwear. At each examination the hand-grip strength was measured with a Martin Vigorimeter (Enraf Nonius, The Netherlands), a rubber bulb connected by a short rubber tube to an aneroid type manometer[9]. The bulb can be readily squeezed by the patients even in the immediate postoperative period. The patients sat up and used their dominant hand The mean of three measurements was recorded.

Nitrogen balance

Five of the patients carefully recorded their complete oral intake while in hospital, and they continued to record their intake by weighing all their food after leaving the hospital At home the patients received commercially available deep-frozen food from the hospital (Måltid för en person, Findus Matforum, Bjuv, Sweden), which they ate as their main dish. They were free to supplement this food with food of their own preference if it was weighed and recorded. The recording was supervised by a dietician

The urine was collected under supervision in 24-h aliquots while the patients were in hospital and by the patients themselves in their homes until the 20th postoperative day. The accuracy of the urinary collections was determined by analysis of the excretion of creatinine, which was constant during the period studied. After leaving the hospital the patients returned every third day to deliver the samples. Hydrochloric acid was added to each collecting can as a preservative From each can 10 ml of urine was taken and the samples were stored at −20°C pending analysis.

Muscle biopsies

In vivo muscle protein synthesis was estimated by ribosome analysis of percutaneous muscle biopsy specimens, taken from the lateral portion of the quadriceps femoris muscle using the Bergstrom biopsy needle[10,11]. Approximately 50 mg of muscle tissue was dissected carefully to remove visible fat and connective tissue and then weighed on an automatic electrobalance (Cahn 29, Cahn Instruments, Cenato, California, USA). Within 3 min after sampling the muscle specimens were frozen in liquid nitrogen and stored at −80°C for not more than 5 weeks pending analysis

The techniques used for the isolation of ribosomes and for determining their size distribution have been described in detail previously[11]. In short, the biopsies were homogenized in a standardized manner in a medium containing an RNAase inhibitor After centrifugation at 1500g for 10 min, the pellet was saved for the determination of DNA. The supernatant was ultracentrifuged at 102 000g for 2 h in a 40·2 rotor (Beckman Instruments, Palo Alto, California, USA). The ribosome pellet thus obtained was resuspended A portion of the suspension was layered onto a linear density gradient between 0·4 M and 1 5 M sucrose. After centrifugation in an SW 50·1 swing-out rotor (Beckman Instruments) for 60 min at 149 000g, the gradient was pumped through a continuous flow cuvette and the absorbance was monitored at 260 nm. The peaks representing 80S monoribosomes, 60S and 40S ribosomal subunits, and the area corresponding to polyribosome particles, were identified. The area under the absorbance curve was determined and the percentage of polyribosomes out of the total ribosomes (polyribosomes, monoribosomes and ribosomal subunits) was calculated. The total ribosome concentration was measured using the absorbance at 260 nm. The concentration was expressed as optical density (OD) units per milligram of tissue DNA.

The coefficient of variation of the total ribosome concentration as well as the percentage of polyribosomes was below 6 per cent[12]. The DNA content was analysed by a fluorometric method[13] using salmon DNA as standard.

Statistics

All values are given as mean(s.e.m) except where otherwise indicated. Student's t test for paired samples was used to compare the different observations[14].

Results

The total concentration of ribosomes per mg DNA in skeletal muscle (*Table 2*) had decreased by 27·5(6 6) per cent ($P<0{\cdot}01$) on day 3 as compared with the preoperative value of 100 per cent (*Figure 2*). On days 10, 20 and 30 following surgery the decreases were 44·5(6·5) per cent ($P<0{\cdot}001$), 48·3(8·9) per cent ($P<0{\cdot}001$) and 45·0(8·2) per cent ($P<0{\cdot}01$) respectively, as compared with the original value before the operation. Compared with the third postoperative day, the total ribosome concentration per mg DNA decreased by 14·7(5·6) per cent on day 10, by 17·6(7·1) per cent on day 20 and by 20·4(8·1) per cent on day 30 after surgery ($P<0{\cdot}05$). The relative proportion of polyribosomes in the total content of ribosome particles (*Table 2*) had decreased by 20·4(6·4) per cent on the third postoperative day ($P<0{\cdot}05$) and by 20·4(3·9) per cent on the tenth postoperative day ($P<0{\cdot}01$) as compared with the preoperative value of 100 per cent (*Figure 2*). On the 30th day after surgery the proportion of polyribosomes had increased by 34·8(13·6) per cent compared with the third postoperative day ($P<0{\cdot}05$).

The nitrogen balance was calculated for 24 h periods from the nitrogen content of the oral intake based on the patients' own recordings, the measured urinary nitrogen losses and the extrarenal nitrogen losses estimated to be 30 mg/kg/day. For the individual patients the daily nitrogen balance was negative for between 3 and 7 days after operation (median value 5 days). The cumulative nitrogen balance was calculated each day for the individual patients and the mean value was lowest on day 5 after surgery (*Figure 3b*).

These nitrogen losses in the immediate postoperative period were not completely restored until the 18th day (median) after surgery (range 8 to >20 days). The energy intake was calculated for 24 h periods based on the patients' own recording of their oral food intake. The habitual caloric intake of the individual patients estimated as the mean intake during postoperative days 10–20 was reached between the second and 12th day after surgery (median seventh postoperative day; *Figure 3a*)

The subjective fatigue score increased by 4·1(0·7) arbitrary units (a.u.) on the third postoperative day compared with the preoperative level ($P<0{\cdot}001$, *Figure 4*) On days 10, 20 and 30 after surgery the increase in subjective fatigue was 2·4(0·8) a.u. ($P<0{\cdot}05$), 1·7(0·6) a.u. ($P<0{\cdot}05$) and 1·1(0 5) a.u. ($P<0{\cdot}05$) respectively compared with the original preoperative value Compared with day 3 after operation the subjective fatigue

Table 2 *The total ribosome concentration, the percentage of polyribosomes in total ribosomes and the polyribosome concentration after surgery in patients undergoing elective cholecystectomy*

	Preoperative	Day 3	Day 10	Day 20	Day 30
Total ribosome concentration (OD/mg DNA)	81·8(8·8) (*n*=9)	56·1(4·3)* (*n*=9)	44·1(5·5)**† (*n*=9)	40·2(7·9)*† (*n*=8)	38·5(4·3)**† (*n*=7)
Polyribosome proportion (%)	46·0(2·3) (*n*=8)	36·2(2·9)* (*n*=8)	36·0(2·8)** (*n*=6)	44·1(3·2) (*n*=6)	52·3(6·0)† (*n*=6)
Polyribosome concentration (OD/mg DNA)	36·4(3·5) (*n*=8)	19·9(2·6)** (*n*=8)	17·8(3·0)** (*n*=6)	19·6(3·1)*** (*n*=6)	21·2(2·6)* (*n*=6)

Values are mean(s.e.m.). Asterisks denote significant differences from the paired preoperative values, $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}01$ and $^{***}P<0{\cdot}001$ respectively. † Denotes significant difference from the paired values on day 3, $P<0{\cdot}05$. OD, optical density

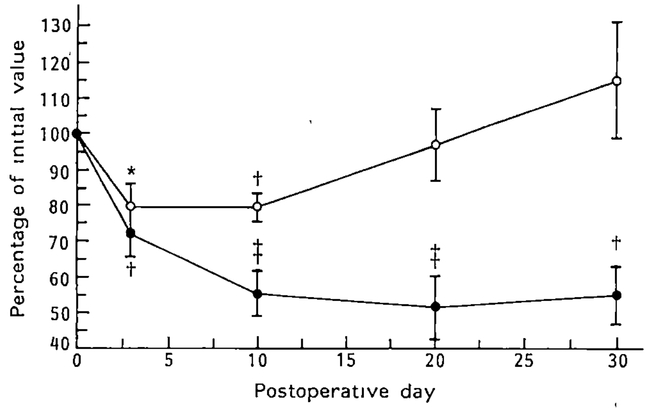

Figure 2 *The total ribosome concentration per mg of DNA (●) and relative proportion of polyribosomes (○) after operation in patients undergoing cholecystectomy* (n=9). *The values are expressed as a percentage of the preoperative value of 100 per cent. Data are given as mean(s.e.m.).* P *values denote significant differences from the paired values on day 0,* *P<0·05, †P<0·01 *and* ‡P<0·001 *respectively. Note that the scale of the y-axis starts at 40 per cent*

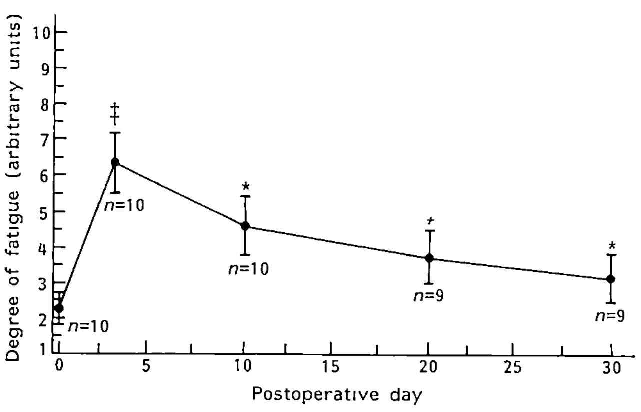

Figure 4 *The subjective feeling of fatigue after operation as estimated by a visual analogue scale in patients undergoing cholecystectomy* (n=9). P *values denote significant differences as compared with the paired preoperative values,* *P<0·05 *and* ‡P<0·001 *respectively. Data are given as mean(s.e.m.)*

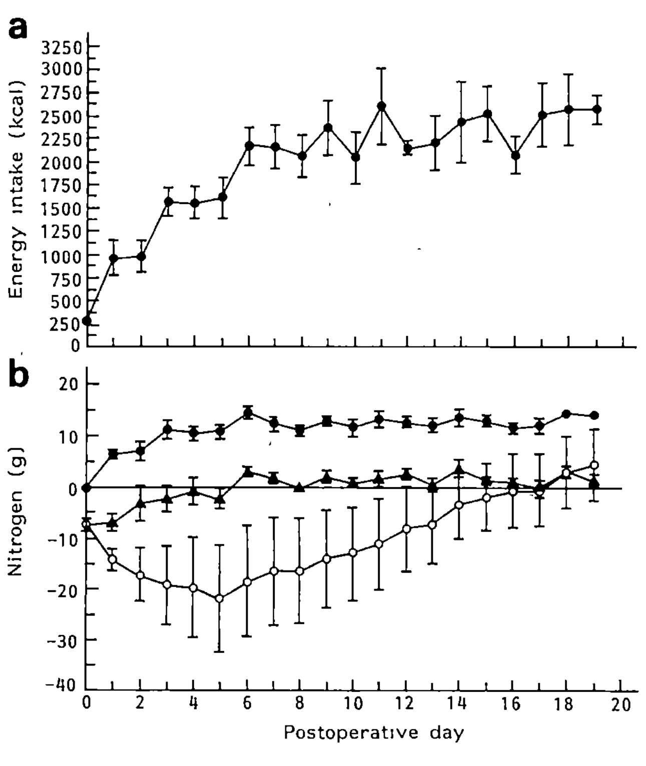

Figure 3 **a** *The energy intake (kcal/24 h) and* **b** *nitrogen intake (g/24 h) (●), nitrogen balance (g/24 h) (▲) and cumulated nitrogen balance (g) (○) for 20 days after operation in patients undergoing cholecystectomy* (n=5). *The nitrogen balance was calculated from the nitrogen content of the oral food intake based on the patients' own recordings, the measured urinary nitrogen losses and the extrarenal nitrogen losses estimated to be 30 mg/kg/day. Data are presented as mean(s.e.m.)*

score had decreased by 1·7(0·7) a.u. on day 10 ($P<0{\cdot}05$), by 2·5(0·7) a.u. on day 20 ($P<0{\cdot}01$) and by 3·1(0·6) a.u. on day 30 ($P<0{\cdot}001$) after surgery. Four out of nine patients regained their preoperative score on the 30th postoperative day. The weight of the patients decreased by 3·4(0·4) per cent on the third postoperative day ($P<0{\cdot}001$), by 3·5(0·3) per cent on the tenth postoperative day ($P<0{\cdot}001$), by 3·3 (0·4) per cent on the 20th postoperative day ($P<0{\cdot}001$) and by 2·0(0·5) per cent on the 30th postoperative day ($P<0{\cdot}01$), compared with the preoperative value set to 100 per cent (*Table 3*). On day 30 after surgery a weight increase of 1·4(0·2) per cent compared with day 3 ($P<0{\cdot}001$), of 1·6(0·3) per cent compared with day 10 ($P<0{\cdot}001$) and of 1·1(0·3) per cent compared with day 20 ($P<0{\cdot}01$) after surgery was noted. However, only one out of nine patients had regained his preoperative weight by the 30th postoperative day. Hand-grip power increased by 5·7(2·0) per cent ($P<0{\cdot}05$) on the tenth postoperative day compared with the third day following surgery, with the original preoperative value set to 100 per cent (*Table 3*). No other significant changes were noted in hand-grip strength.

Discussion

Protein synthesis in skeletal muscle decreases following elective abdominal surgery and, using ribosome analysis, we have characterized these changes over 30 postoperative days. The total concentration of ribosomes decreased by almost 50 per cent and no signs of restoration were seen up to 30 days after surgery. The relative proportion of polyribosomes decreased by 20 per cent in the immediate postoperative period and returned to normal by day 20. The subjective fatigue scores of the patients increased after operation and were not normal by 30 days. The nitrogen balance was negative immediately after the operation and cumulated nitrogen losses were not compensated for until after 18 days.

Table 3 *Weight and hand-grip strength after operation in patients undergoing elective cholecystectomy*

	Preoperative ($n=10$)	Day 3 ($n=10$)	Day 10 ($n=10$)	Day 20 ($n=9$)	Day 30 ($n=9$)
Weight	67·1(5·2)	64·8(4·9)***	64·8(4·9)***	65·3(5·4)***	66·1(5·5)**‡§
Hand-grip strength (%)	100	100·1(2·8)	105·8(3·2)†	99·3(3·5)	100·9(3·0)

Values are mean(s.e.m.) Asterisks denote significant differences from the paired values on day 0, **$P<0·01$ and ***$P<0·001$ respectively † denotes significant difference from the paired values on day 3, $P<0·05$. ‡ denotes significant difference from the paired values on day 20 and § denotes significant difference from the paired values on days 3 and 10, $P<0·01$ and $P<0·001$ respectively

Determination of the concentration and size distribution of ribosomes is the only available technique for assessing muscle protein synthesis *in vivo* in man by repeated measurements[6,11,15–18]. The total ribosome concentration reflects the capacity for protein synthesis, while the relative proportion of polyribosomes assesses the activity of protein synthesis[19–24]. The technique is qualitative in character and the reproducibility and reliability of the results rests upon a high and constant harvest of ribosome particles[25,26]. On the third day after elective abdominal surgery the total ribosome concentration and the percentage of polyribosomes declines, regardless of whether or not total parenteral nutrition (TPN) is provided[6,15,17,18]. In the present study these findings were extended by showing that the total concentration of ribosomes per milligram of DNA remained low during the 30 postoperative days studied. Starvation for 3 days produces a decline in the total ribosome content of skeletal muscle and refeeding for 2 days prevents a further decrease in the ribosome population, but does not increase the low level in healthy volunteers[11,16] or in growing rats[26].

In our study the relative abundance of polyribosomes remained low until 10 days after surgery. On day 20 the percentage of polyribosomes had been restored to the preoperative level, indicating efficient utilization of the ribosome population for protein synthesis The total content of ribosomes in muscle declined until the tenth postoperative day and remained low on the 30th day following surgery, suggesting a long-standing depression of the size of the machinery for muscle protein synthesis. Fasting in healthy volunteers reduces the relative proportion of polyribosomes[11,16]. During refeeding for 2 days after 3 days of fasting the fraction of polyribosomes rises towards the original prefasting level[16]. A limited number of investigations have considered the changes in muscle protein synthesis after elective surgery and demonstrated a decline on the third postoperative day[5,6,15,17,18]. This study addresses the question of when restoration to the original preoperative level of protein synthesis occurs. The results of the ribosome analyses indicate that long-term follow-up studies are indicated when the effects of postoperative nutritional support on muscle protein synthesis are to be evaluated. It is recommended that several different techniques depending on different underlying assumptions are used in parallel to assess protein synthesis.

Cholecystectomy in metabolically healthy subjects is a standardized and well-documented surgical trauma with a fully developed post-traumatic stress response[27–29] The nitrogen balance becomes negative after surgery in non-malnourished subjects. In patients undergoing cholecystectomy the negative nitrogen balance is improved in the early postoperative period by the provision of TPN[6], but equilibrium cannot be attained despite the fact that the amounts of calories and nitrogen are elevated far above the actual requirements[6,30,31]. In such cases overfeeding creates a metabolic burden which is detrimental to the patient[32]

In the present study the cumulated nitrogen losses were not completely restored until the 18th postoperative day. A major portion of the nitrogen excreted is derived from skeletal muscle[2]. The capacity for protein synthesis, as estimated from the total ribosome concentration, had not been restored at the time when the cumulated nitrogen losses had been compensated for, however, a restoration of the relative proportion of polyribosomes was noted, indicating a return of muscle protein synthesis activity to the normal level.

Even uncomplicated abdominal surgery is followed by a pronounced feeling of fatigue, which may persist for more than 1 month after operation[7,8] The score for the subjective feeling of fatigue increased threefold on the third day after surgery, and five out of nine patients did not regain their preoperative score by the 30th postoperative day. Major abdominal surgery is reported to be associated with a reduction in hand-grip strength[9,33]. This was not demonstrated in this homogeneous patient group undergoing abdominal surgery of medium scope, raising the question of whether the method is sensitive enough to separate a decline in muscle function from greater skill acquired with repetitive examinations. The body-weight decreased following surgery but on the 30th postoperative day one out of nine patients had regained their preoperative weight. Postoperative fatigue may be due to deterioration of cardiovascular function, neuromuscular performance and nutritional status rather than being dependent upon psychological factors[34]. Fatigue after elective surgery seems to be unpredictable from the preoperative status of the patient, but correlates with weight loss and decrease in maximum force and endurance in elbow flexors and is related to deterioration of the nutritional status[8,35–37].

There is no correlation between duration of anaesthesia and postoperative fatigue and fatigue is independent of both preoperative state-anxiety and trait-anxiety, which suggests somatic rather than psychological factors to be involved[34,35]. No direct biochemical correlation with the clinical state of postoperative fatigue exists. The content of energy-rich phosphogens[38] and the oxidative capacity[39] in skeletal muscle are not affected by elective surgery. The sustained depression of the total ribosome content of skeletal muscle is the first biochemical parameter described that has shown a time pattern similar to that of the subjective fatigue.

In conclusion, elective abdominal surgery caused a depression of protein synthesis for over 30 days, a longer period than previously known. Although the postoperative tiredness certainly has a multifactorial background, the very slow restoration of the capacity for muscle protein synthesis seems to be an important factor. Furthermore the results suggest that long-term follow-up is desirable when the effect of different postoperative nutritional regimens are to be evaluated.

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Constipation: another indication for restorative proctocolectomy

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We have extended our experience of restorative proctocolectomy and ileoanal anastomosis to include 13 patients with functional bowel disorders. Eight had recurrent constipation after colectomy for slow transit constipation and five had constipation and overflow incontinence associated with megarectum and megacolon. In all cases the only alternative was a permanent stoma. Despite a high complication rate, 11 patients (85 per cent) felt that the operation had been worthwhile with improvement of their symptoms and quality of life. The operation led to a mean frequency of defaecation of 4·8 times (range 2–8) during the day, and 1·2 times (range 0–4) during the night. There was no frank incontinence and, while only one patient experienced soiling during the day, six patients suffered from night-time soiling. Two patients have had the pouch converted to an ileostomy due to persistent complications and a poor functional result.

Keywords: Constipation, restorative proctocolectomy

Patients with severe constipation present a difficult problem. Current surgical therapy for severe, long-standing, idiopathic constipation is total colectomy with ileorectal anastomosis. However, approximately 10 per cent of these patients develop recurrent severe constipation with abdominal pain and bloating[1]. Ileal reservoir and pouch–anal anastomosis may provide an acceptable alternative to end ileostomy for relief of the symptoms of recurrent constipation. A second group, patients with primary megarectum and megacolon, may have a reasonable functional result using the Soave or Duhamel reconstruction[2]. If megarectum is associated with megacolon, restorative proctocolectomy and pouch–anal anastomosis provides an alternative to construction of a permanent stoma.

Patients and methods

Thirteen patients with functional bowel disorder underwent restorative proctocolectomy and ileoanal anastomosis (*Table 1*) Hirschsprung's disease had been excluded in all cases Eight of these patients were young women (age 25–45 years) with slow transit constipation who had had a previous subtotal colectomy or colectomy and ileorectal anastomosis All eight complained of severe constipation associated with abdominal pain and bloating despite their previous surgery and four of the eight had developed a megarectum subsequent to the initial surgery. A further five patients (age 16–66 years) complained of constipation and overflow incontinence as a result of megarectum associated with megacolon.

All patients were assessed by videoproctography and measurements of rectal emptying, pelvic floor function, sphincter reflex and sphincter pressure (*Table 1*). Rectal sensation was absent in those patients with megarectum.

Eleven patients had formation of a J pouch, nine of whom had a temporary covering ileostomy. Two patients had a W pouch, both with temporary covering ileostomy In patients with megarectum the length of the anal canal was short and the gross megarectum made cross-stapling of the anal canal impossible. A hand-sutured ileoanal anastomosis proved necessary

Results

Complications

Five of the eight patients with slow transit constipation made a good recovery with no complications Three had episodes of small bowel obstruction of whom two required laparotomy and subsequently developed ileoanal stenosis requiring dilation before the pouch was finally converted to an ileostomy.

Three of the five patients with megarectum and megacolon had no complications. Two had an anastomotic leak requiring drainage. One of these developed small bowel obstruction requiring repeated hospital admission and the other made a full recovery. In all patients with megarectum bowel preparation was impossible because of faecal impaction in the dilated rectum.

Functional result

Follow-up ranged from 2 months to 6 years (mean 20 months). Two patients had the pouch removed and an end ileostomy formed following persistent complications and a poor functional result. At maximum follow-up the mean frequency of defaecation was 4·8 times (range 2–8) during the day, and 1·2 times (range 0–4) during the night. There was no frank incontinence, and while only one patient experienced soiling during the day, of the 13 patients, six suffered from night-time soiling. Seven patients required antidiarrhoeal medication and seven were able to discriminate flatus from faeces. The functional results are summarized in *Table 2*

Symptomatic improvement

Eleven patients obtained complete relief of constipation and the preoperative symptoms of pain, bloating and abdominal distension. Whilst some patients were disappointed with the result, 11 of 13 patients felt that the operation had been worthwhile and had improved their quality of life

Discussion

Restorative proctocolectomy with ileoanal anastomosis is now a well established treatment for patients with ulcerative colitis and familial adenomatous polyposis[3] Nicholls and Kamm reported the use of this operation to treat two patients with functional bowel disorders[4] One patient had a dramatic improvement in bowel function whilst the other, although improved, still required catheterization to evacuate the pouch.

The present results deal with two groups of patients with functional bowel disorders for whom the only alternative was a permanent stoma In three patients with primary megarectum not associated with megacolon (unreported results) a colonic pouch with coloanal anastomosis produced excellent early results with no complications. However, all patients described in this report had gross colonic dilatation making colonic preservation inappropriate

Although there was a high complication rate, it should be remembered that many of these patients were undergoing

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Table 1 *Initial diagnosis and preoperative assessment*

Patient no.	Diagnosis	Previous surgery	Sphincter pressures		Rectoanal inhibitory reflex	Pelvic floor movement	Ability to evacuate 150 ml balloon
			Rest (mmHg)	Squeeze (mmHg)			
1	Slow transit constipation	Ileorectal anastomosis; pelvic floor division	–	–	Absent	Normal	Yes
2	Slow transit constipation	Ileorectal anastomosis	–	–	Normal	Normal	Yes
3	Slow transit constipation	Subtotal colectomy	90	230*	Absent	Normal	No
4	Slow transit constipation	Ileorectal anastomosis	80	120*	Absent	Normal	No
5	Slow transit constipation	Right hemicolectomy; ileorectal anastomosis	120	300*	Absent	Normal	No
6	Slow transit constipation	Ileorectal anastomosis	100	200*	Normal	Normal	Yes
7	Slow transit constipation	Ileorectal anastomosis	110	250†	Normal	Normal	Yes
8	Slow transit constipation	Subtotal colectomy	100	250†	Normal	Normal	Yes
9	Megarectum with megacolon	Rectopexy, myomectomy	100	200†	Absent	Normal	No
10	Megarectum with megacolon	Nil	120	200†	Absent	No movement	No
11	Megarectum with megacolon	Nil	110	200†	Absent	No movement	No
12	Megarectum with megacolon	Nil	100	220†	Absent	Normal	No
13	Megarectum with megacolon	Nil	120	300†	Absent	Normal	No

* Postoperative; † preoperative

Table 2 *Results following pouch formation*

Patient	Frequency		Urgency	Soiling		Antidiarrhoeal medication	Ability to discriminate
	Day	Night		Day	Night		
1*	6	4	No	No	Yes	Yes	No
2†	6	0	No	No	No	Yes	No
3	6	3	No	No	Yes	Yes	No
4	6	1	Yes	Yes	Yes	Yes	No
5	2	0	No	No	No	No	Yes
6	4	1	No	No	No	No	Yes
7	2	1	No	No	No	No	Yes
8	5	1	No	No	No	Yes	Yes
9	5	1	No	No	No	No	Yes
10	8	2	No	No	Yes	Yes	No
11	5	1	No	No	Yes	Yes	Yes
12	5	0	No	No	Yes	No	No
13	3	0	No	No	No	No	Yes

* Pouch removed at 12 months because of poor function and repeated episodes of small bowel obstruction, † ileostomy formed at 2 years because of severe ileoanal stenosis

complicated surgery for at least the second time. In those with megacolon and/or megarectum bowel preparation was often impossible The dilated rectum filled the pelvis making excision difficult and in two patients the bladder was also grossly enlarged. The alternative for all these patients was a permanent stoma which itself is often associated with small bowel obstruction. The functional results in six patients were good or excellent allowing them to lead a normal active life with acceptable frequency of defaecation and no incontinence Eleven of the 13 patients felt the operation had been worthwhile and had improved their quality of life. These results compare favourably with those for patients undergoing standard surgical procedures for constipation and are not dissimilar to those for restorative proctocolectomy and ileoanal anastomosis for ulcerative colitis and familial adenomatous polyposis^5.

Restorative proctocolectomy and ileoanal anastomosis may provide an acceptable alternative to stoma formation in carefully selected patients with failed ileorectal anastomosis for slow transit constipation and for patients with primary megacolon associated with megarectum if the symptoms warrant further surgical intervention.

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Manovolumetric and sensory characteristics of the ileoanal J pouch compared with healthy rectum

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Pouch volume, motility, sensory function and integrated pouch–anal mechanisms during graded isobaric distension of the pouch were prospectively studied in 67 patients with a J pouch–anal anastomosis. The findings were related to functional outcome. Thirty-six normal controls were studied for comparison. In contrast with normal rectum, the ileal pouch exhibited pronounced motility, and pouch contractions were frequent even at a high distension pressure. The presence of high pressure motility was associated with a poor functional outcome. The threshold pressure and threshold volume for eliciting first sensation of filling and urge to defaecate were significantly higher in the ileal pouch. The pressure threshold levels were not related to the functional outcome. Sphincter inhibition on pouch distension reappeared in 25 per cent of the patients. The distension pressure required to elicit the inhibition was considerably higher than in the control subjects. The functional result was similar irrespective of whether sphincter inhibition was present or not. The motor and sensory function of this artificial setting appear to be controlled by nervous mechanisms that are different from those in the healthy anorectum.

Keywords: Pelvic ileal pouch, manovolumetry, motility, sensory function, rectoanal inhibition

A number of studies on pouch and sphincter function have been performed in an attempt to define the physiological and anatomical determinants of the clinical outcome after restorative proctocolectomy with a pelvic pouch. Impaired resting anal tone and a low volume non-compliant neorectum are among the main factors that have been considered responsible for a poor pouch function[1–3]. Several pouch designs are on trial at present and different techniques are employed for the perineal phase of the operation in an attempt to improve results[4–7]. The relative roles of other factors have only been investigated to a limited degree

The extensive operative procedure which involves mucosal stripping of the anal canal and replacement of the rectum proper with an ileal substitute is likely to damage both the motor and the sensory components of the complex integrated autonomous nervous arrangements controlling the anorectum; such factors may have a considerable impact on function.

The aim of the present study was to compare rectal and pouch volume and motility characteristics in response to graded isobaric distension, and to study the sensory function with particular interest focused on the rectoanal and pouch–anal reflex function. A further objective of the study was to determine if any of these modalities might have a direct influence on the functional result in pouch patients

Patients and methods

Sixty-seven patients (32 women), mean age 35 years (range 17–59 years) with well established J pouches were studied prospectively Sixty-three patients were operated upon for ulcerative colitis and four for familial polyposis. Data were compared with those obtained from a control group of healthy volunteers, $n = 36$ (19 females), mean age 31 years (range 23–42 years). The study was approved by the Ethical Committee of the University of Goteborg

The patients were operated on by the same group of surgeons and according to routines described previously[8,9] including an endoanal mucosectomy and a handsewn anastomosis The mean(s d) length of ileal segments used for construction of the reservoir was 16(3) cm, range 12–30 cm

Anorectal/pouch manovolumetry was performed using a technique allowing for simultaneous recording of anal pressure and rectal/pouch volume in response to graded isobaric distension of the rectum/pouch with a non-compliant balloon[9,10]. After a test insufflation with a distension pressure of 40 cmH_2O, the investigation was continued as a series of distensions with 5 cm increments up to 20 cmH_2O, and thereafter with 10 cmH_2O increments to the maximum tolerated pressure or maximum pressure allowed by the distension device used which was 80 cmH_2O. The balloon was emptied between each distension, which was maintained for 1 min Since the controls did not tolerate a distension pressure of 80 cmH_2O the last increment had to be omitted

Rectal/pouch volume was defined as maximum volume recorded during distension. Rectoanal reflex sphincter inhibition was defined as a 20 per cent reduction of resting anal pressure and disappearance of spontaneous anal motility During each distension the patients were told to report when the first sensation of pouch filling and subsequently when the urge to defaecate was experienced. The corresponding pressure and pouch volumes at which these sensations were felt were recorded and referred to as 'first sensation' and 'urge' respectively

All patients were investigated with manometry before operation, before closure of the loop ileostomy and at 1, 3, 6, 12 and 24 months after ileostomy closure Recording of the number of bowel movements and occurrence of soiling was based on self-monitoring diaries kept for 2 weeks before each visit.

The patients were asked if they could discriminate and safely release flatus They were also asked to define in detail the nature of the urge to defaecate. Functional variables were listed according to an arbitrary score designed to quantify the overall functional result: score range 0–16; patients with good overall function scored 0 points, those with poor function a maximum of 16 points[8,9] If not otherwise stated, the results are based on the 2-year follow-up in 58 patients

Results are presented as mean(s d). Statistical analysis included Student's *t* test comparing means. Correlations were sought using linear regression analysis

Results

Volume and motility

On distension with 40 cmH_2O normal rectal volume amounted to 243(48) ml, range 155–322 ml (*Figure 1*). Compliance

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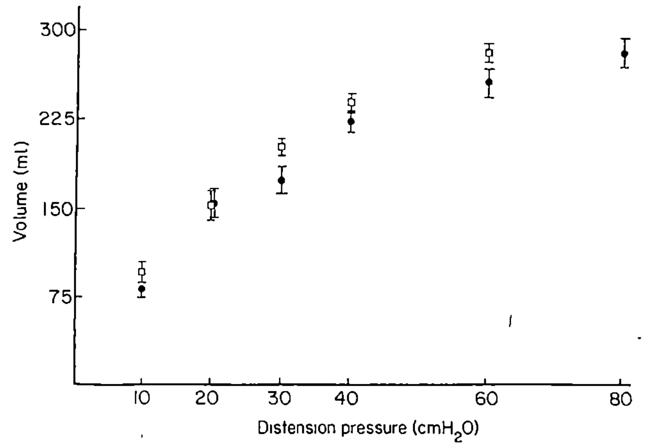

Figure 1 *Rectal (□) and pouch (●) volume at increasing distension pressures also allowing estimation of compliance in the pressure intervals. Values are mean(s.e.m.)*

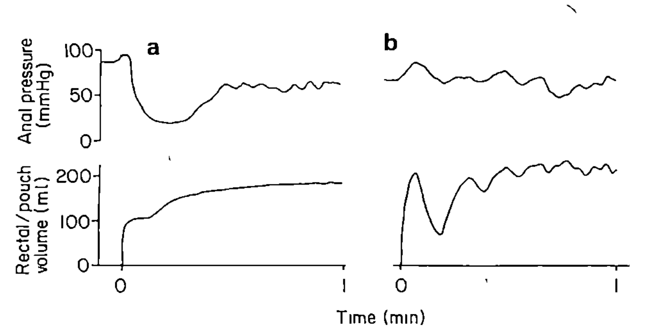

Figure 2 *Typical resting anal pressure and volume expansion on distension (40 cmH$_2$O) of* **a** *rectum and* **b** *the pelvic J pouch. Note the pronounced motility pattern and lack of reflex sphincter inhibition in the pelvic pouch*

amounted to 8·0(2·8) ml/cmH$_2$O in the pressure interval 0–20 cmH$_2$O with a decrease in compliance at higher pressure intervals. Rectal distension caused an initial rapid volume expansion followed by a transient reflex contraction as reflected by a volume decrease lasting for about 10 s (*Figure 2*). This phase was in turn followed by a gradual volume increase until cessation of the distension. The volume displaced by the rectal contraction varied with the distension pressure but was maximal at 27(6), range 15–40 cmH$_2$O amounting to about 10 per cent (18(13) ml) of the final volume. Successive contractions were observed in 64 per cent of the subjects but were mostly of lower amplitude than the initial one. However, on distension of the rectum with a pressure exceeding 50 cmH$_2$O contractions were only occasionally seen.

The volume of the ileal pouch was 221(88) ml, range 65–440 ml, when distended at a pressure of 40 cmH$_2$O and did not differ significantly from the rectal volume (*Figure 1*). Pouch compliance was similar to rectal compliance. The immediate volume increase observed on distension of the ileal pouch was followed by a more pronounced and long-lasting reflex contraction, displacing a maximum of 35 per cent (76(53) ml) of the pouch volume at a distension pressure of 41(17) cmH$_2$O, range 10–80 cmH$_2$O (*Figure 2*). Irregular successive high amplitude contractions sometimes displacing a larger volume than the initial one were observed in 90 per cent of the pouches. Moreover, 75 per cent still exhibited a reflex contraction at a distension pressure of 80 cmH$_2$O. The motility pattern of the pouch in individual patients was similar throughout the follow-up. No specific pattern was observed in 18 patients who had suffered from pouchitis.

Sphincter inhibition

The rectoanal inhibition reflex was present in all controls and before operation in all patients. The pressure threshold for eliciting the reflex was 12(3) and 17(9) cmH$_2$O, respectively. Sphincter inhibition, which was absent in all patients during the first postoperative months, reappeared subsequently in 15 patients: in three patients within 6 months of operation, in three within 12 months and in nine within 24 months. Their mean age was significantly lower than that of those without inhibition, (29 *versus* 37 years, $P<0\cdot05$). The motility pattern on pouch distension was similar in patients with and without recovery of this response. Although strikingly similar to the rectoanal reflex inhibition seen before operation, the distension pressure (and hence the volume) needed to elicit the response was higher in patients than in controls (34(22) cmH$_2$O, $P<0\cdot05$), and also higher when compared with preoperative figures for patients, $P<0\cdot05$.

Perception

The rectal volume necessary to elicit the first sensation of rectal filling and the urge to defaecate exhibited great variation. Thus, perception of filling was recorded at 68(55) ml, range 11–238 ml and perception of urge at 138(68) ml, range 26–285 ml. The threshold pressure for first sensation of rectal filling was 12(3) cmH$_2$O, range 5–15 cmH$_2$O and coincided with the threshold for rectoanal inhibition. Urge to defaecate was experienced at 28(11) cmH$_2$O, range 15–50 cmH$_2$O, i.e. close to the pressure for maximal reflex contraction.

The volume needed to elicit first sensation of pouch filling or urge to defaecate varied greatly, being 178(92) ml, range 52–435 ml and 239(92) ml, range 80–445 ml, respectively; both were larger than in the rectum, $P<0\cdot001$. The pressure level required to elicit first sensation of filling of the ileal pouch was also higher than in the rectum, $P<0\cdot001$, and amounted to a mean of 33(15) cmH$_2$O, range 15–60 cmH$_2$O. When analysed at 1 month after surgery one-third of the patients experienced no sensation of urge, even when a distension pressure of 80 cmH$_2$O was used, and 20 per cent of the patients still failed to experience this sensation at the 1 year follow-up. At 2 years, however, 50 of the 58 patients (86 per cent) claimed that they experienced urge to defaecate, but the sensation was elicited at a higher distension pressure (63(15) cmH$_2$O, range 30–80 cmH$_2$O, $P<0\cdot001$) and volume (239(92) ml, range 80–445 ml) compared with the controls (*Figure 3*).

When interviewing patients more specifically regarding these sensory modalities, the majority stated that they were unable to specify the sensation calling them to defaecate. Twenty-four patients referred to a vague abdominal discomfort or a feeling or suprapubic distension combined with borborygmia, while 18 patients described a poorly defined pressure sensation deep

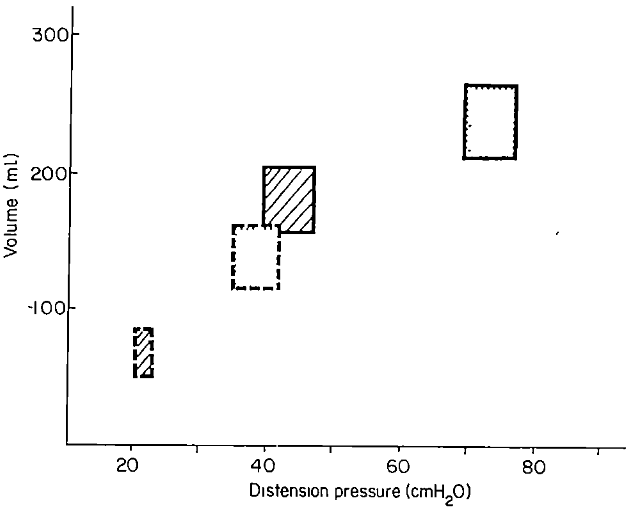

Figure 3 *The 95 per cent confidence intervals for pressure and volume thresholds when sensation of filling (▨) and 'urge' (□) was experienced at distension of the normal rectum (- - -) and the ileal pouch (——). Note the high pressure and volume required to elicit sensations in the patients*

in the pelvis. Only 22 patients stated that the sensation was similar to that experienced before they had their disease. Moreover, the subjective sensation experienced on pouch distension was not always equal to the sensation that called them to defaecate in their daily life.

Manovolumetric data as related to functional outcome

When analysing the motility pattern at the 1 year follow-up, patients with reflex contractions at high distension pressure ($\geqslant 80$ cmH$_2$O) had a higher day-time evacuation frequency, $P<0.02$, and used a protective pad at night more frequently, $P<0.05$. The overall functional result as reflected in the functional score was also less satisfactory in these patients (4·7 *versus* 2·5, $P<0.01$). However, at 2 years these differences failed to reach statistical significance.

Although the overall functional results in terms of score points tended to be more favourable in patients exhibiting reflex inhibition (score 3·0 *versus* 4·4), this difference was not statistically significant. Patients with reflex sphincter inhibition on pouch distension suffered from soiling to a similar extent as the others and the sensory thresholds were also similar. Thirty-seven patients (64 per cent) claimed they were able to release flatus safely. The ability to do so was independent of the presence of reflex inhibition.

The volume recorded at the first sensation of pouch filling was directly related to maximum pouch volume and correlated with the functional results. The pressure threshold for the first sensation of filling, however, correlated neither to the individual functional variables nor to the functional score, and no correlation was found between 'urge' thresholds and function. In fact, patients with suprapubic or undetermined vague localization of the 'urge' signal had a lower day-time evacuation frequency, suffered less from soiling and had a significantly better overall function (score 3·2 *versus* 4·7, $P<0.05$).

Discussion

The results of the present study imply similarities between the normal rectum and the well established pelvic J pouch with regard to both volume and compliance. Whilst the similarity in volume capacity is in concert with other investigations[1,11], the data on pouch compliance vary over a wide range[1,2,12–14]. Differences in definition and methodology may be the main reasons for this divergence.

Despite these similarities of volume and compliance, the rectum and the ileal pouch exhibited marked differences in response to graded distension. The motility was more pronounced in the ileal pouch and J pouches often displayed contractions even at high distension pressures. Patients exhibiting this motility pattern had a poor functional result, while those in whom such contractions were absent exhibited a low evacuation frequency, less soiling and had a superior overall functional score. This observation is in agreement with previous reports, implying that the distension volume at which high pressure waves are generated may be the important functional determinant[1,12,15]. The observation also reflects a fundamental physiological difference between the normal rectum and the ileal substitute. While the healthy rectum can accommodate increasing volumes with insignificant and/or occasional motor contractions, the ileal J pouch lacks this physiological property of receptive relaxation.

According to traditional physiology[16] the sensory zone in the upper anal canal and the rectoanal inhibitory reflex together allow sensory 'sampling' which is considered to play a major role in the fine control of continence. Controversy still exists as regards the fate of reflex sphincter inhibition after mucous proctectomy[6,17]. Moreover, it has not been resolved whether its disappearance will influence the functional outcome[18]. The present study shows that reflex inhibition was abolished after surgery, which is in keeping with previous reports[5,6,13]. Sphincter inhibition reappeared with the passage of time in 25 per cent of the patients and similar observations have been reported by others[19]. The pathways of the reflex have been debated. Lane and Parks[20], who reported on sphincter inhibition in patients subjected to rectal excision and coloanal sleeve anastomosis, suggested that the internal anal sphincter tone was influenced via the intrinsic neural plexus of the colon directly across the anastomosis. Other possibilities might be activation of extrinsic reflex pathways or even, as suggested by Grant *et al.*[6], simply an experimental artefact. The observation in the present study that the pressure threshold needed to elicit sphincter inhibition was higher than in controls, and probably outside the normal physiological range, might support the latter view. It is possible that patients in whom sphincter inhibition was present suffered from soiling similar to those lacking the reflex and the ability to release flatus safely was also independent of reflex inhibition.

The sensations of rectal filling and call to defaecation are thought to be mediated within the sacral parasympathetic nerves and constitute another facet of anorectal function of the utmost importance for continence and normal defaecation. According to traditional teaching the site of origin of the stimulus producing the rectal type of sensation is located in receptors within the rectal wall[21], whereas recent authors claim that such receptors might also be located in the pelvic floor musculature[20,22]. In the present study fundamental differences were demonstrated between the ileal pouch and the healthy rectum. Both the distension volume and the pressure level required to elicit the sensation of pouch filling were significantly higher than in the rectum, and the perception of urge to defaecate was also elicited at a higher pressure in patients than in controls. Similar observations on pressure and volume thresholds have been reported by others[1,11]. Moreover, the quality of the sensation perceived as the urge to defaecate often differed considerably from normal.

The present results cast doubt on the hypothesis that the receptors necessary for the perception of rectal filling and urge to defaecate are located in the levator ani[20,22]. The different threshold pressure demonstrated in the present study would imply a nerve fibre set with other neurophysiological properties, such as pain fibres or sympathetic visceral afferents. The fact that a substantial proportion of pouch patients were either unable to specify the sensation calling them to defaecate or stated that they experienced a vague intra-abdominal discomfort or pain would support such a view. Similar modalities were also described by Goligher and Hughes in 1951[21]. It is important to emphasize that awareness of pressure changes in the pouch as experienced by patients appeared not to influence the functional result.

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Coeliac artery compression syndrome: the effect of decompression

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The effects of operation to decompress the coeliac artery were evaluated in 11 consecutive patients with coeliac artery compression syndrome. Immediately after the operation all patients were free of symptoms. Three months later three of the 11 had recurrent abdominal pain. Long-term follow-up between 15 and 23 years, obtained by questionnaire, was available for eight patients. All eight had return of symptoms similar to those before surgery. These unsatisfactory results suggest that operation should not be undertaken in patients with vague upper abdominal complaints and compression of the coeliac artery by the median arcuate ligament, who do not otherwise have pathological conditions which might explain their symptoms.

Keywords: Coeliac artery, decompression operation, follow-up, complaints

In the 1960s and early 1970s patients with chronic upper abdominal symptoms and compression of the coeliac artery were often treated by decompression of the artery after other causes of symptoms had been eliminated.

In the early 1970s several authors demonstrated that long-term results of this operation were unsatisfactory[1,2]. Discouraged by these reports, the last coeliac artery decompression operation at this institution was performed in 1974. However, in the middle 1980s other authors reported long-term results of coeliac decompression which supported the existence of the compression syndrome and a favourable outcome after treatment[3–6]. In an attempt to shed further light on this syndrome and the results of surgical therapy this paper evaluates the long-term clinical results of coeliac artery decompression.

Patients and methods

The records of all nine women and two men who underwent a coeliac artery decompression operation for treatment of chronic upper abdominal pain at this institution between 1962 and 1974 were reviewed. All patients had been selected for decompression on the basis of chronic upper abdominal pain only after angiography had demonstrated a solitary coeliac artery stenosis of at least 95 per cent diameter. In all patients other common diseases causing upper abdominal pain had been eliminated as far as possible. Those eliminated were gallbladder disease, peptic ulceration, chronic pancreatitis and gastro-oesophageal reflux. The mean age of the patients at the time of operation was 41·0 years (range 14–60 years). Long-term follow-up was achieved by questionnaire Results were classified as clinical success or failure. Criteria for success were relief of upper abdominal symptoms and weight gain at the time of maximum follow-up in conjunction with a low operative morbidity and mortality rate.

Relevant preoperative patient characteristics are listed in *Table 1*. All 11 patients had protracted abdominal pain localized in the upper half of the abdomen. The pain was discontinuous in eight patients, radiating in five and provoked by eating in five. Weight loss was observed in seven patients. The mean weight loss was 6 kg (range 3–10 kg) during a mean period of 55 months (range 6–118 months) Symptoms had persisted during a mean period of 57 months (range 6–106 months)

Physical examination was performed in all patients and an upper abdominal bruit, whose characteristics were not changed by deep inspiration, was auscultated in nine. Abdominal palpation revealed only non-specific upper abdominal tenderness in four patients.

Preoperative assessment consisted of routine haematological tests, radiographs of the chest, abdomen, upper gastrointestinal tract and gallbladder, and a gastroduodenoscopy. If these were all normal a biplanar aortic angiogram was performed which showed a coeliac artery stenosis of at least 95 per cent diameter in all patients The superior mesenteric artery and the inferior mesenteric artery were normal

Examination of the abdomen during operation excluded other intra-abdominal pathology In all patients decompression of the coeliac artery was performed by transection of the median arcuate ligament and complete resection of the coeliac plexus. In four patients peroperative intraluminal coeliac artery blood pressure was measured and showed a gradient over the stenosis which varied from 15 to 40 mmHg. In these patients the pressure gradient in the coeliac artery vanished after decompression.

After operation, symptoms were relieved in all 11 patients The mean duration of hospital admission was 14 days (range 11–23 days). Postoperative angiography of the decompression site was not performed

Results

The results of short-term (3 months after operation) and long-term follow-up are shown in *Table 2*. After the short-term interval eight patients had no symptoms and three had recurrent symptoms identical with those existing before surgery. Long-term follow-up was available for only eight patients, as two had died and one was not available. Mean follow-up for these eight patients was 19·1 years (range 15–23 years). After the long-term interval all eight patients had recurrent symptoms identical with those present before coeliac artery decompression. Symptoms recurred after a mean of 6·8 years (range 0–20 years). Body-weight had increased by between 2 and 10 kg in six patients, but it had decreased by 1 and 5 kg respectively in the other two. Because of persisting disabling symptoms five patients underwent one or more laparotomies after the coeliac artery decompression operation without any success These operations included division of adhesions (three patients), hysterectomy (two patients), ovariectomy (two patients), cholecystectomy (two patients), appendicectomy (two patients) and splenectomy (one patient). Six patients required a continuous regimen of analgesic or tranquillizer to relieve their symptoms.

Discussion

This retrospective study has shown beneficial short-term results but poor long-term results for transection of the median arcuate ligament and resection of the coeliac plexus. The operative mortality rate was zero; the operative morbidity rate was negligible. While six of the eight patients showed an increase in weight at long-term follow-up, it is difficult to consider weight gain as a beneficial effect of the operation because weight naturally increases during an interval of 20 years. More importantly, symptoms were not relieved in any of the patients at final follow-up. These poor results corroborate those of

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Table 1 *Preoperative characteristics of 11 patients with coeliac artery compression syndrome*

Patient no.	Age (years)	Upper abdominal pain	Symptoms provoked by eating	Weight loss	Upper abdominal bruit	Upper abdominal tenderness
1	14	+	–	–	+	–
2	60	+	+	+	+	–
3	57	+	–	+	+	–
4	60	+	–	–	+	–
5	56	+	+	+	+	+
6	37	+	+	+	+	+
7	18	+	–	–	+	–
8	35	+	–	+	+	+
9	37	+	+	+	–	–
10	25	+	–	–	–	–
11	57	+	+	+	+	+

Table 2 *Follow-up results in 8 patients with coeliac artery compression syndrome*

Patient no	Symptoms after 3 months	Follow-up (years)	No years free of complaint	Weight gain (kg)	Abdominal reoperations	Continuous medication
4	–	15	5	+2	+	–
5	+	17	0	+10	+++	+
6	+	17	0	−5	+++	+
7	–	17	14	−1	–	–
8	–	20	1	+6	+	+
9	–	22	20	+5	–	+
10	–	22	14	+6	–	+
11	+	23	0	+3	++++	+

others[2,7]. Szilagyi reviewed the entire literature of the coeliac artery compression syndrome and demonstrated that no patient had ever been proven, on scientific grounds, to have had an abnormality of intestinal structure or function which was caused by extraluminal compression of the coeliac artery. He suggested that the supposed relief from operation was nothing other than a placebo effect[8].

Nevertheless, good results of coeliac artery decompression have been reported[5,9–14], but most of these reports are flawed by short follow-up and small numbers of cases. However, two recent studies, with carefully selected patients and long term follow-up, have also supported the existence of the coeliac artery compression syndrome[4,6]. In contrast to these studies, which reported beneficial results in both the short and long-term, patients in the present study did not have reconstruction of the coeliac artery. This could be important because coeliac artery reconstruction might diminish the propensity for re-stenosis in the long term. However, it cannot be the explanation for the short-term return of symptoms in patients in whom the pressure gradient was relieved without any need for reconstruction.

Stanley and others have suggested that a steal phenomenon from the superior mesenteric to the coeliac bed might be the explanation for the non-specific symptoms of coeliac artery compression syndrome[13,15,16]. This is unlikely because there is voluminous clinical and experimental evidence that long-standing isolated obstruction of one of the intestinal arteries is compensated for by collateral circulation from both other arteries without symptoms[2,17–20]. It has also been suggested that neurogenic stimuli produced by throbbing of the compressed artery against the coeliac plexus might explain the vague upper abdominal complaints[9,21]. While in the present group of patients the coeliac plexus was resected, the poor long-term result might still be explained by hypertrophy of the unexamined remainder of the coeliac plexus tissue, but this could not explain the short-term return of symptoms.

Perhaps the reason for the present poor long-term results lies in the prolonged follow-up, the mean of which is twice as long as the longest yet reported[4] In three patients (38 per cent) symptoms returned after 14, 14 and 20 years respectively

In conclusion, while the recent literature has demonstrated some good results for operation for coeliac artery compression syndrome, the present study has failed to confirm this in a group of patients with a postoperative follow-up of nearly 20 years. Explanations for this difference may lie in the operative procedure, or in the prolonged follow-up of the present study. The aetiology of the syndrome, if it actually exists, is still unknown, and although both vascular and neurological hypotheses have been postulated, these are unlikely. The results and discussion presented here suggest that operation should not be undertaken in patients with vague upper abdominal complaints and compression of the coeliac artery by the median arcuate ligament, who do not otherwise have a pathological condition to explain their symptoms.

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Case report

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Sweet's syndrome: a severe complication of pneumococcal vaccination following emergency splenectomy

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We report the first case of acute febrile neutrophilic dermatosis (Sweet's syndrome), following the use of a new 23-valent pneumococcal vaccine after splenectomy.

Case report

A 36-year-old woman underwent an emergency splenectomy for delayed rupture following blunt trauma 4 weeks before admission. Six units of whole blood were transfused and her condition was stable during the early postoperative period. Benzylpenicillin (250 mg b.d.) was commenced immediately after the operation for long-term prophylaxis. She was given an injection of 23-valent pneumococcal vaccine (Pneumovax, Morson, Hoddesdon, UK) on the second postoperative day. Four hours later she developed a pyrexia of 38·6°C (*Figure 1*) which was initially thought to be due to a chest infection (which was not confirmed subsequently) and was treated with physiotherapy and erythromycin. Over the next 4 day, she had a swinging pyrexia up to 39°C associated with a leucocytosis up to 27×10^9/l (71 per cent neutrophilia). There was no overt focus of infection and a routine infective screen, including blood cultures, viral titres and abdominal ultrasound, was normal. A chest radiograph showed a small left pleural effusion consistent with splenectomy. In view of the continuing concern of possible sepsis ampicillin was added to the antibiotic regimen on postoperative day 6. Over the following 24 h she developed multiple, tender, indurated, erythematous plaques over the distal upper and lower limbs, leading to a provisional diagnosis of an erythema multiforme-like reaction secondary to antibiotic therapy. The antibiotics were discontinued but her condition continued to deteriorate with persistent fever and rigors. The rash became more florid and confluent, extending to the upper trunk and thighs with some lesions developing bullae. A clinical diagnosis of Sweet's syndrome was then made and confirmed with incisional biopsy of a discrete lesion (*Figure 2*).

Her pyrexia resolved within 12 h of commencing prednisolone (60 mg/day) on the 11th postoperative day and the rash gradually subsided over the next few days. Her condition relapsed when the prednisolone was reduced to 30 mg/day on day 19, but remitted when the dose was increased again to 40 mg/day on day 21. Thereafter, steroid therapy was gradually reduced and she currently remains in remission 4 months after the illness, on a daily dosage of 10 mg prednisolone.

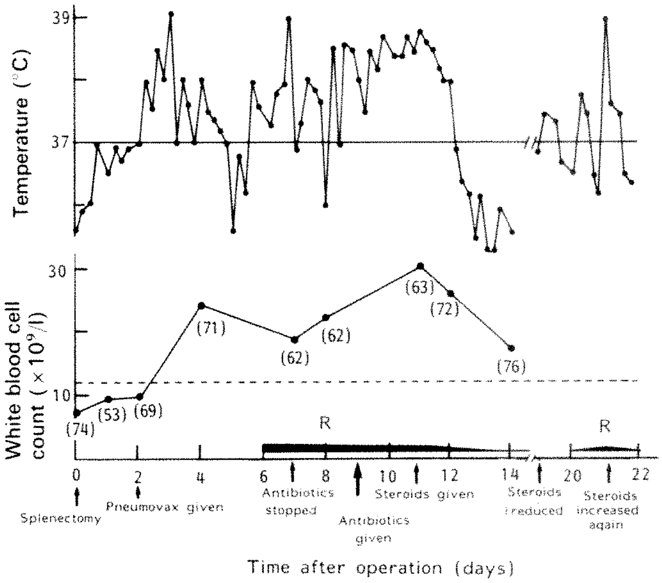

Figure 1 *Graph depicting clinical course of patient together with the parameters of white blood cell count and body temperature following emergency splenectomy and instigation of steroid therapy. Values in parentheses are percentage neutrophils.* ■, *rash;* R, *rigor*

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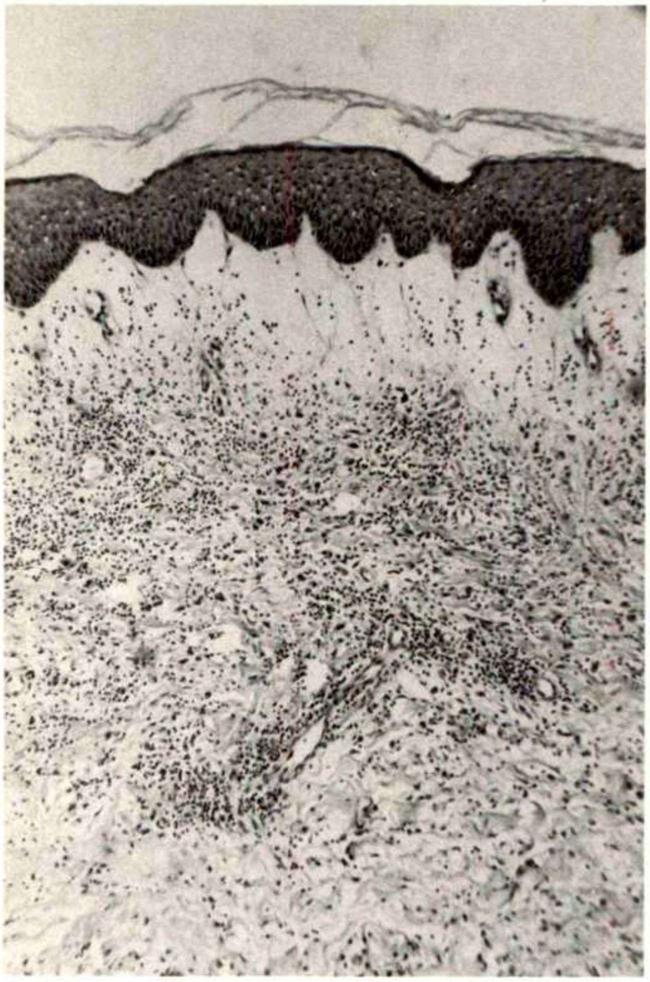

Figure 2 *Sweet's syndrome. Photomicrograph of the skin biopsy demonstrating marked oedema of the papillary dermis with intense neutrophilic infiltrate throughout the upper dermis and focal spongeosis in the centre of the lesion*

Discussion

Sweet's syndrome is a rare but distinctive illness characterized by fever, neutrophilic leucocytosis and indurated painful plaques on the limbs, face and neck. Early skin lesions resemble erythema multiforme clinically but histological features are characteristic.

The aetiology of Sweet's syndrome is unclear. Cases have been described following upper respiratory tract infection, 'flu-like' illness, smallpox and BCG vaccination and as a consequence of myeloid leukaemia[1–3]. A steroid-responsive, acute febrile systemic reaction has been described following pneumococcal vaccination after splenectomy[4]. This may have been an early manifestation of the syndrome, which was treated empirically with steroids, but a formal diagnosis was not made.

In this patient the diagnosis of Sweet's syndrome proved to be a difficult and protacted one, hinging on the histology of a discrete lesion. This difficulty in clinical diagnosis may explain why the syndrome has only recently been differentiated from other dermatoses, such as erythema multiforme. However, the marked female preponderance, swinging high pyrexia and peripheral neutrophilic leucocytosis along with the typical features of the rash should suggest the diagnosis and lead to early biopsy. This is necessary to confirm the diagnosis before treatment with high-dose corticosteroids which bring about a prompt relief of cutaneous and systemic symptoms, as in this case.

The long-term risk of overwhelming sepsis after splenectomy has led to the recommendation of routine pneumococcal vaccination following this procedure[5]. A new 23-valent pneumococcal vaccine has recently become available and has superseded the 14-valent vaccine as it confers a broader range of resistance to pneumococcal infection. We are unaware of any previous reports of Sweet's syndrome following pneumococcal vaccination but with the now routine use of this vaccine following splenectomy we would advise clinicians to be aware of this severe complication.

Acknowledgements

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Late outcome of undersewing alone for gastric ulcer haemorrhage

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Between 1977 and 1988 22 patients requiring urgent surgery for bleeding gastric ulceration were managed by simple undersewing of the ulcer. Long-term follow-up of these patients was undertaken to determine the risk of recurrent gastric ulceration and further gastric ulcer haemorrhage. Two patients died in the immediate perioperative period leaving 20 patients available for long-term follow-up (mean 43·3 months). Three recurrent gastric ulcers were diagnosed, two of these presenting with haemorrhage. No patient presented with further gastric ulceration while on histamine (H_2) receptor antagonist therapy. The long-term outcome of undersewing alone, when combined with maintenance H_2-receptor antagonist therapy, is satisfactory in terms of low mortality and low risk of ulcer recurrence.

Keywords: Gastric ulcer, haemorrhage

Surgery for gastric ulcer haemorrhage carries a high mortality rate. The standard surgical procedures of gastrectomy and truncal vagotomy with drainage are associated with perioperative mortality rates of 13–45 per cent[1–3].

This high mortality rate can be attributed primarily to death from concomitant disease in an elderly population[2]. In recent years there has been a move towards less radical surgical procedures and the rationale of undersewing alone is to achieve haemostasis with no attempt to perform a definitive ulcer healing procedure.

While undersewing alone appears to be an effective method of achieving haemostasis with a low operative mortality rate[1], reservations have been expressed about the risks of ulcer recurrence and haemorrhage in the longer term[4,5]. We have therefore obtained follow-up on a group of patients managed by simple undersewing.

Patients and methods

The patients in this study have been reported previously[1]. Between 1977 and 1988, 566 patients with haemorrhage from a gastric ulcer were managed by the Haematemesis Management Team at the Western Infirmary. Of these patients 83 (15 per cent) required urgent surgery for significant re-bleeding and, of these, 22 were managed by simple undersewing and biopsy of the bleeding ulcer, comprising 27 per cent of all operations for gastric ulcer haemorrhage. The operative procedures performed were chosen at the discretion of each surgeon and the group managed by undersewing alone were not selected because of poor risk factors as judged by age or transfusion requirements[1].

There were two perioperative deaths, both due to cardiorespiratory disease, and there was one recurrent haemorrhage in the immediate perioperative period which resolved without further surgical intervention. Twenty patients with a mean age of 64·8 years (range 32–82 years) were discharged from hospital and were therefore available for long-term follow-up. Hospital records were obtained and letters were circulated to the patients and appropriate general practitioners to obtain information on current state of the patient's health, with particular reference to dyspeptic symptoms, recurrent ulceration and H_2-receptor antagonist prescription. In cases where patients had died during the period of follow-up the cause of death was ascertained from the hospital records or from the Greater Glasgow Health Board Information Services Unit. Follow-up was until January 1989 or death.

Results

The mean period of follow-up was 43·3 (range 3–121) months. With the exception of two patients who died 3 months after surgery all patients were followed up for at least 1 year (mean = 47·7 months). There were eight deaths in total, none due to gastric ulceration (*Table 1*).

One patient had a persistent gastric ulcer which had not healed after 4 months of ranitidine therapy. The patient in question suffered from severe rheumatoid arthritis and was concurrently taking indomethacin which may have been relevant to failure of ulcer healing.

Two patients developed recurrent gastric ulcer haemorrhage, one after 3 months and the other after 3 years. Neither patient was taking H_2-receptor antagonist therapy at the time of the second haemorrhage. One patient required further surgery to control the haemorrhage, while the other settled with conservative management. In the former, who re-bled 3 months after the original operation, the second procedure was undersewing of the ulcer followed by long-term H_2-receptor antagonist therapy. The latter patient died of advanced gastric carcinoma 3 years after surgery. This tumour was at a site distant to the previous ulcer and it is unlikely that a malignant ulcer was misdiagnosed at surgery. The use of H_2-receptor antagonists is summarized in *Table 2*. H_2-receptor antagonists were used with increasing frequency and for longer periods in the latter part of the study period and since 1985 indefinite maintenance with H_2-receptor antagonists has become routine. Since this policy was adopted there have been no recurrent ulcers following simple undersewing.

Table 1 *Cause of death in eight patients*

Cause of death	Age (years)	Time elapsed since surgery (months)
Renal failure	70	3
Meningitis	48	3
Bronchial carcinoma	87	15
Respiratory failure	69	26
Gastric carcinoma	63	36
Pharyngeal carcinoma	86	42
Pulmonary fibrosis	85	50
Respiratory failure	69	86

Table 2 *H_2 antagonist therapy after surgery in 20 patients*

Duration of treatment	Number of patients
0	2
2–6 months	11
Long-term	7

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Discussion

The original publication from this unit detailed the immediate outcome of simple undersewing, highlighting the low mortality rate when compared with the more conventional treatments of gastrectomy and truncal vagotomy with drainage. This has been borne out by Schein and Gecelter[6] who have shown a low mortality rate for undersewing even in high risk patients. While it seems self-evident that the primary objective in the operative management of gastric ulcer haemorrhage is to control the haemorrhage, simple undersewing without a definitive ulcer healing operation has been regarded as inadequate treatment because of the supposed high risk of recurrent ulceration and further haemorrhage[4,5]. As a result of this scepticism most reports include only small numbers of patients treated by undersewing and there is a tendency to employ the technique only in patients who are deemed unfit to withstand more radical and more prolonged surgical procedures[7,8]. Not surprisingly in some reports mortality has been high and information on the longer term outcome has been difficult to obtain.

It is now clear that the arguments against simple haemostatic surgery for bleeding gastric ulceration have been overcome by the availability of many effective ulcer healing agents. In particular, H_2-receptor antagonist therapy has been demonstrated to be effective in modifying the complications of peptic ulceration and can be administered safely over a long period of time[8,9]. Indeed this therapy after non-definitive surgery for peptic ulcer perforation has been associated with decreased morbidity and mortality rates[10].

In the present group of patients, recurrent gastric ulcer haemorrhage outside the immediate perioperative period occurred in 10 per cent. Haemorrhage was not seen, however, in any patient taking an H_2-receptor antagonist and there has been no late haemorrhage since maintenance H_2 antagonist therapy was introduced in 1985. One non-healing ulcer was identified without further haemorrhage in a patient treated with both ranitidine and indomethacin, a problem which has been well recognized previously[11].

Another obvious concern is the possibility of inadvertently managing a malignant ulcer in this way. It is routine practice in our unit to biopsy these ulcers at the time of surgery and, to date, no unrecognized malignant ulcers have been identified histologically. One gastric carcinoma developed during the period of follow-up, but the time interval and the site of the tumour were against the possibility of malignancy in the undersewn ulcer.

In conclusion, long-term follow-up does not demonstrate an undue risk of further complications following undersewing of a bleeding gastric ulcer. It would seem wise, however, to manage these patients after operation with long-term H_2-receptor antagonist therapy.

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Late sequelae of penetrating cardiac injuries

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Fifty-four patients who survived a penetrating cardiac injury were assessed for late cardiac complications. The mean follow-up after injury was 23 months. Clinical history and physical examination suggested cardiac complications in nine patients (17 per cent). Electrocardiogram was abnormal, but usually not diagnostic, in 17 (31 per cent). Routine two dimensional Doppler echocardiography revealed abnormalities in 17 (31 per cent). Ten patients (19 per cent) had valvular or septal defects. Other abnormalities included pericardial effusion, ventricular and septal dysfunction, and ventricular dilatation. Although it is impossible to determine how many of these abnormalities were post-traumatic, it seems that the incidence of late sequelae of cardiac injuries is high, and it is recommended that routine late follow-up of these patients should be done. Assessment should include routine echocardiograms.

Keywords: Cardiac injuries, sequelae

The incidence, type, and natural history of late sequelae following penetrating injuries of the heart are not well established. The literature on this subject is scanty, and to the authors' knowledge no prospective study with routine late echographic cardiac evaluation has been done. In the present study this problem is investigated in a series of 54 patients.

Patients and methods

Fifty-four patients who survived a penetrating injury of the heart were traced and investigated for any anatomical or functional cardiac abnormalities. All patients had been subjected to an emergency thoracotomy and cardiac injury repair. The time interval from injury to follow-up ranged from 1·5 months to 12 years (mean of 23 months). Cardiac assessment included; (1) clinical history, (2) clinical examination, (3) electrocardiogram (ECG), and (4) Doppler echocardiography. Some patients were further investigated by cardiac catheterization. There were 52 men and 2 women, with ages ranging between 13 and 48 years (mean of 23 years). The cause of injury was a knife in 53 patients and a bullet in one. The records of all patients were reviewed for any cardiac abnormalities detected during the early postoperative period.

Results

Clinical history

Five patients (9 per cent) gave a history suggestive of a cardiac problem. However the ECG and/or echographic investigations confirmed cardiac abnormalities in only three patients (*Table 1*).

Clinical examination

Review of the records showed that clinical examination in the early postoperative period had detected an abnormality in only one patient. He had had a pansystolic murmur, and echogram and cardiac catheterization had revealed a small ventriculoseptal defect (VSD). The late clinical examination was performed by a cardiologist and it was abnormal in seven patients (13 per cent). In six patients the echogram confirmed a valvular lesion or a VSD and in one patient no abnormality was found (*Table 2*).

Electrocardiogram

The ECG was abnormal in 17 patients (31 per cent). In three there was right bundle branch block, in one right ventricular strain, and in one myocardial ischaemia. In the remaining 12 patients the abnormalities were not specific.

Doppler cardioechogram and cardiac catheterization

These investigations revealed anatomical and/or functional abnormalities in 17 patients (31 per cent). In 10 patients there were valvular or septal defects of which seven patients had mitral valve incompetence, one patient tricuspid valve incompetence, and two patients VSD. Other detected abnormalities included ventricular dilatation (three patients), ventricular dysfunction (four patients), septal hypokinesia (two patients), and pericardial effusion (one patient). Only one of these patients had injury to the coronary vessels (peripheral left anterior descending artery).

Treatment

None of the patients in this series required surgical treatment. However two had medical treatment (one for cardiac failure and one for ischaemia). Asymptomatic patients with echographic abnormalities will be followed up.

Discussion

The majority of patients with penetrating cardiac injuries die before reaching any medical care. In a study of 532 such patients[1], 77 per cent were dead on arrival at hospital, the overall mortality rate was 83 per cent and the operative mortality rate was 14·4 per cent. Patients with intracardiac injuries (i.e. septal defects, valvular lesions) had less chance of surviving and the incidence of intracardiac shunts was 4·3 per cent in fatal cases, compared with 2·2 per cent in survivors[1].

The incidence, nature, and natural history of post-traumatic cardiac sequelae are not well established. It is well known that small intracardiac defects may escape clinical examination during the early postoperative period. Many of these lesions may become clinically detectable only at a later stage, when the defect becomes larger after resolution of the surrounding oedema or after lysis of an occluding coagulum plug, and when enlargement of the ventricle (and thus the defect) occurs[1]. Furthermore, clinical examination alone infrequently detects functional abnormalities such as ventricular dysfunction or ischaemia. The incidence of cardiac abnormalities in the early postoperative period varies markedly in different series, and depends on the criteria used for the selection of patients for further investigation by cardioechogram and/or catheterization. In two series from this institution, echographic and catheterization examinations were performed only on patients presenting with murmurs, and the incidence rate of intracardiac lesions was 2·2 per cent[1,2]. In the present study the incidence

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Table 1 *Patients with symptoms* (n = 5)

Patient no.	Months after injury	Symptom	Clinical examination	ECG	Echogram
1	24	Chest pain	Normal	Normal	Mild LV dysfunction
2	35	Dyspnoea on exertion	Normal	Non-specific changes	Mild RV dysfunction
3	72	Dyspnoea	Cardiac failure	Non-specific changes	LV dysfunction
4	4	Chest pain	Normal	Normal	Normal
5	4	Chest pain	Normal	Normal	Normal

ECG, electrocardiogram; LV, left ventricle; RV, right ventricle

Table 2 *Patients with abnormal clinical examination* (n = 7)

Patient no.	Months after injury	Clinical diagnosis	ECG	Echogram
1	72	Cardiac failure	Non-specific abnormalities	LV dysfunction
2	36	Mild TI	Normal	Mild MI
3	1·5	Pan-systolic murmur	RV strain	TI, dilated RV
4	34	Mild MI	Right BBB	Mild MI
5	6	Mild TI	Right BBB	Mild mitral prolapse
6	11	Mitral prolapse	Non-specific abnormalities	Mitral prolapse
7	13	Small VSD	Normal	Normal

ECG, electrocardiogram; TI, tricuspid valve incompetence; MI, mitral valve incompetence; VSD, ventricular septal defect; BBB, bundle branch block; RV, right ventricle

rate of shunts detected during the early postoperative period was 1·9 per cent. Mattox *et al.*[3] investigated only patients with symptoms or abnormality on physical examination between one and 20 days after admission. They reported an incidence rate of 3·9 per cent for fistula and intracardiac shunts, but many other cardiac abnormalities were detected echocardiographically with an overall incidence rate of 23·4 per cent. The same authors reported that gunshot wounds were more likely to result in intracardiac abnormalities than knife injuries. From the review of the English literature no study was found where routine echocardiography and/or catheterization studies were performed on all patients in the early postoperative period.

For the reasons mentioned above, late follow-up of these patients is important. Clinical history and examination are not adequate. In the present series clinical history alone was diagnostic in only 6 per cent, clinical examination alone in 11 per cent, and both combined in 17 per cent. Routine cardioechogram revealed cardiac abnormalities in 31 per cent of patients. Fallahnejad *et al.*[4] investigated 20 symptomatic patients and found eight secondary cardiac complications; however, when 9 patients were investigated routinely, 7 were found to have a cardiac abnormality. Symbas[5] reviewed 56 patients who survived a cardiac injury, with a minimum follow-up of 6 months, and he found an incidence of 25 per cent of delayed cardiac sequelae, 37 per cent for gunshot injuries and 19 per cent for knife injuries. The routine work up of these patients was based on clinical examination, chest radiograph and ECG. It is quite possible that a number of abnormalities were missed because echocardiography was not performed.

It is probable that many cardiac abnormalities that were detected by ECG were not caused by trauma. The incidence of mitral valve prolapse in the general population is quite high, and rheumatic heart disease in low socioeconomic groups is common. Despite this, it seems that the incidence of post-traumatic cardiac sequelae is high, and routine late follow-up of these patients is indicated. The advent of Doppler echocardiography has made the investigation of these patients easy as it is non-invasive and gives accurate anatomical and functional information on the heart[6].

Delayed sequelae of cardiac injuries include: intracardiac defects (atrio- and ventriculoseptal defects, valvular incompetence), vascular-cardiac fistula, ventricular aneurysms, conduction abnormalities, ventricular dysfunction or dilatation or hypertrophy, endocarditis, and pericarditis[1,3,4,7]. The natural history of many of these lesions is not known. Some VSDs may close spontaneously[2,8] and experimental studies have shown that traumatic VSDs may close many months after injury[9,10]. Many of the more minor abnormalities may be managed expectantly, although surgical correction may be indicated in patients with symptoms or cardiac enlargement[10]. Some patients may become symptomatic many years after injury[10–12]. In the present series no patient required an operation but two were treated medically. However, over a period of 8 years, the cardiac surgeons at this institution have operated on 31 patients with post-traumatic cardiac defects, all of them in cardiac failure[11]. Even less is known of the natural history of other abnormalities such as conduction abnormalities, ventricular dysfunction, and hypertrophy and dilatation, although many of these defects may lead to a shorter life-span. Regular follow-up of patients will allow early detection of those requiring treatment, thus reducing patient discomfort and even death. However many of the victims are from a low socioeconomic background and may seek medical help only in advanced stages.

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Abdominocervical (transhiatal) oesophagectomy in the management of oesophageal carcinoma

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Fifty-four patients have undergone abdominocervical oesophagectomy for oesophageal carcinoma as an alternative to a conventional transthoracic approach. Their median age was 69 years, with a range of 38–90 years, and 39 per cent of patients had chronic cardiorespiratory disease. Lymph node metastases were found in 80 per cent of patients and transmural tumour spread in 91 per cent. Median duration of operation was 2·2 h (range 1·75–6·0 h), and median transfusion requirement was 2·5 units (range 0–8 units). Respiratory complications were common (41 per cent) and caused all six postoperative deaths (11 per cent). Other complications were atrial fibrillation (26 per cent), transient recurrent laryngeal nerve palsy (11 per cent), cardiac failure (2 per cent), stroke (2 per cent), subphrenic abscess (2 per cent) and empyema (2 per cent). There were two anastomotic leaks (4 per cent), clinically manifest as temporary salivary fistulae. There have been 32 deaths from recurrent carcinoma, with a median duration of survival of 14 months (range 4–53 months). Fifteen patients are still alive, with a median survival of 16·5 months (range 3–49 months); the current 3-year survival rate is 10 per cent. All patients resumed normal swallowing after operation, but 11 of them developed anastomotic strictures requiring a median of three dilatations. Avoidance of formal thoracotomy by the abdominocervical approach may allow more rapid oesophagectomy without increasing the risk of postoperative death and gives a quality of palliation at least equivalent to that of conventional transthoracic oesophageal excision.

Keywords: Oesophageal carcinoma, oesophagectomy, transhiatal, abdominocervical

The 5-year survival rate is less than 5 per cent for patients with carcinoma of the oesophagus[1,2]. Although conventional oesophageal resection achieves some cures, it may be associated with an appreciable morbidity rate (10–46 per cent) in patients who are often elderly and infirm[3,4]. Mortality rates vary quite widely in different centres, ranging from zero to 28 per cent with a median around 10–12 per cent[3–7]. Neither radical *en bloc* resection nor the use of adjuvant therapy have improved the long-term survival statistics[5,8–10]. Radiotherapy, chemotherapy, intubation and laser recanalization provide palliation in some patients, but they carry their own complications (some of which are lethal) and subsequent swallowing is poorer than that provided by palliative resection or bypass[6].

One reason for conventional oesophagectomy in the elderly being such a major undertaking is that formal thoracotomy restricts postoperative respiratory excursion, provoking atelectasis and chest infection. Moreover, a multicavity approach and the necessity to reposition the patient prolongs operating time and magnifies the physiological insult. By avoiding thoracotomy, the abdominocervical (transhiatal) route has the potential to reduce operating time and cardiorespiratory complications, thus allowing surgical palliation to be extended to a larger number of patients with oesophageal cancer. Recent reports from specialist oesophageal centres indicate that morbidity and mortality rates with this procedure are at least equivalent to those obtained using the transthoracic approach[11–13]. Whether abdominocervical oesophagectomy is a safe procedure in the hands of surgical gastroenterologists with an interest in oesophageal disease is an issue that has not been previously addressed.

Since 1981 abdominocervical oesohagectomy has progressively replaced transthoracic oesophagectomy as the operation of choice for carcinoma of the oesophagus in the hospital Departments of Surgery at Bristol and Bath.

Patients and methods

Fifty-four patients underwent abdominocervical oesophagectomy for carcinoma of the oesophagus between March 1981 and December 1988 at the Bristol Royal Infirmary and the Royal United Hospital, Bath, UK. The age range of the group was 38–90 years, with a median of 69 years and an equal sex distribution. In all cases a diagnosis was made by endoscopy and biopsy, and distant metastases were sought by computed tomography or ultrasound scan and chest radiography. Patients with known distant metastases were excluded from operation, and these patients were usually treated by endoscopic intubation. As there are other surgeons and physicians in our institutions who treat oesophageal carcinoma, an accurate overall resectability rate is not known. Of those referred to our departments, some 60 per cent will undergo resection. Histologically 26 (48 per cent) were squamous cell carcinomas, and 28 were adenocarcinomas. Thirty-five tumours (65 per cent) were sited in the lower third of the oesophagus, 17 (31 per cent) were in the middle third and there were two upper-third lesions. Twenty-one patients (39 per cent) had chronic intercurrent cardiorespiratory disease as defined by electrocardiography, chest radiography or pulmonary function tests, and a requirement for chronic drug therapy. Eighty per cent were smokers. All patients considered fit enough to undergo general anaesthesia on the basis of these investigations were offered operation. Old age was not necessarily an exclusion criterion: indeed, eight patients were over the age of 80 years.

Dysphagia was the presenting symptom in 93 per cent of cases, and the median duration of symptoms was 3 months (range 0·5–14·0

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Table 1 *Complications of abdominocervical oesophagectomy*

Respiratory infection	22 (41)
Deaths	6 (11)
Recurrent laryngeal nerve palsy	6 (11)
Anastomotic leak	2 (4)
Atrial arrhythmia	14 (26)
Pulmonary embolism	2 (4)
Subphrenic abscess	1 (2)
Empyema	1 (2)
Congestive cardiac failure	1 (2)
Cerebrovascular accident	1 (2)

Values in parentheses are percentages

months). Pain was experienced by 15 (28 per cent) patients, and 50 per cent had weight loss amounting to > 10 per cent of body-weight. Preoperative preparation included intensive chest physiotherapy and correction of anaemia, but parenteral or enteral hyperalimentation was not routine.

Our operative technique for abdominocervical oesophagectomy has previously been described[14]. It is based on the description by Orringer and Sloan[15], using an upper midline incision in the abdomen and a right medial supraclavicular incision in the neck. An attempt was made to identify and protect the recurrent laryngeal nerve early during the neck dissection, avoiding traction on the tracheo-oesophageal groove. The hiatus was usually incised anteriorly to facilitate access to the lower mediastinum and, where the tumour was adherent to the diaphragm, a cuff of right crus was excised with the specimen. A lighted retractor was useful to facilitate dissection under direct vision within the lower posterior mediastinum, but above this level the manipulation was performed blindly from below. The anastomosis was performed in one layer of continuous or interrupted sutures of Prolene® (Ethicon Ltd., Edinburgh, UK) or Vicryl® (Ethicon Ltd.), and a pyloroplasty was routine. The gastric fundus was not anchored to the prevertebral fascia. Cervical and abdominal suction drains were always inserted and, for the last 3 years bilateral, intercostal drains have generally been placed at the end of the operation.

An arterial line is a prerequisite for close monitoring of systolic pressure during blunt dissection behind the heart. This part of the operation is carried out in stages, as cardiac filling is impeded by the surgeon's hand and transient hypotension is the rule. All patients had a thoracic epidural catheter inserted for postoperative analgesia, and selected patients (17 per cent) were ventilated overnight following operation. Most patients were extubated at the end of the operation and were returned to the ward for postoperative care. In 15 patients a jejunal feeding tube was placed at the end of the procedure, jejunostomy feeding commencing at 48 h. Oral feeding followed radiological confirmation of anastomotic integrity, usually at 5–7 days.

Follow-up data have been obtained on all patients. Active investigation for recurrence has not been a routine part of follow-up and has only been instigated for appropriate symptoms. Recurrence has been assessed by chest radiography, computed tomography and ultrasound scan plus biopsy in some cases. Autopsy was performed in a third of the deaths.

Results

The median duration of operation was 2·2 h, with a range of 1·75–6·0 h, and median blood transfusion requirement was 2·5 units (range 0–8 units). Of 54 patients, six died in the postoperative period (30-day mortality rate of 11 per cent), each as a result of pneumonia (*Table 1*). Overall, 22 patients (41 per cent) had radiological evidence of pulmonary collapse or consolidation, and in 17 of them pathogens were cultured from the sputum. Three cases of pneumonia required tracheostomy and a period of ventilation. In six patients temporary recurrent laryngeal nerve palsy was encountered, one patient requiring tracheostomy for stridor. Two patients had a leak at the anastomosis, both manifesting as salivary fistulae. Neither patient had sepsis requiring treatment with antibiotics, and both leaks resolved within 3 weeks with conservative management. No other leaks were demonstrated radiologically.

Atrial arrhythmias occurred in 14 patients (26 per cent), all reverting with digoxin therapy; one patient suffered protracted congestive cardiac failure. Non-fatal pulmonary embolism was seen in two patients. A subphrenic abscess in one patient and an empyema in another both resolved following percutaneous tube drainage. Median time until the full establishment of postoperative feeding was 10 days, and median postoperative stay was 15 days with a range of 10–60 days. All patients resumed normal swallowing after operation, but 11 (20 per cent) developed dysphagia due to benign anastomotic stricture, which required dilatation. Generally these strictures have been easy to dilate, requiring outpatient endoscopic bougienage on one to seven occasions (median of three occasions). One patient developed an anastomotic recurrence after 7 months and required intubation.

Forty-three patients (80 per cent) had histological evidence of nodal involvement by metastatic tumour, and 49 (91 per cent) had transmural invasion into surrounding tissues (stage III). Only three patients (6 per cent) had carcinoma confined to the wall of the oesophagus (stages I and II).

Of 48 postoperative survivors 33 have subsequently died, all but one from recurrent carcinoma. The median survival of this group was 14 months with a range of 4–53 months. Twenty-eight patients had distant metastases at death, and 19 of these also had evidence of local recurrent disease. Four patients had local (thoracic or upper abdominal) recurrence at death in the absence of distant metastases. One patient, aged 91 years, died suddenly at 16 months without evidence of recurrent carcinoma. Fifteen patients are currently alive, two with known recurrent disease. The median survival in this group is 16·5 months with a range of 3–49 months. Of the 15 survivors five are still alive beyond 3 years, giving an overall 3-year survival rate of 10 per cent.

Discussion

The results show that abdominocervical oesophagectomy can achieve lasting relief from dysphagia with a mortality rate (11 per cent) that compares with that of several other series of conventional transthoracic resections (10–12 per cent)[6,7,16,17]. Factors known to place patients at increased risk of death after oesophagectomy are age, intercurrent cardiorespiratory disease and extent of the lesion[18]. In this series age did not necessarily form an exclusion criterion. The mean age (69 years) was almost 10 years older than that of several large series of patients undergoing transthoracic oesophagectomy[19–21], and two patients were aged 90 years. Operative mortality rate for oesophagectomy is significantly greater in those over 70 years of age[22] and may reach 71 per cent in those over 80 years[18]. In this series eight patients were aged over 80 years, and all survived.

As many as 40 per cent of our patients had chronic cardiorespiratory disease, which in some cases might have excluded them from consideration for a standard thoracotomy. Well controlled congestive cardiac failure and normal arterial blood gases in patients with chronic respiratory disease were adjudged adequate criteria for offering surgery. Our exclusion criteria were therefore distant metastases with a short life expectancy and local invasion of vital structures. Bronchoscopy is advisable for middle-third lesions. Unfortunately, preoperative computed tomography of the chest was not uniformly reliable in identifying local invasion, and in four cases the resection was abandoned in favour of intubation following a trial dissection. Obvious lymph node metastases did not preclude oesophagectomy, however.

Despite the avoidance of thoracotomy, respiratory complications were common and caused all six deaths. This has been the experience of some others who have used the transhiatal approach (*Table 2*)[23–33], but the wide variation (0–52 per cent) in the incidence of pulmonary complications probably reflects different criteria for definition. We chose a radiological definition of collapse/consolidation because it seems the most objective one. Although six patients died, most of the remaining respiratory complications were minor and resolved with physiotherapy. The use of postoperative thoracic epidural analgesia during the latter part of the series has enabled early

Table 2 *Published reports of abdominocervical oesophagectomy*

Principal author	Year (reference)	No. of patients	Mean age (years)	Mortality rate (%)	Cardiorespiratory morbidity rate (%)	Thoracotomy for haemorrhage*	Postoperative stage (III/IV) (%)	Percentage survival rate	Follow-up (years)
Szentpetry	1979[23]	17	63	6	0	0	–	–	–
Garvin	1980[24]	10	54·3	0	50	0	60	–	–
Steiger	1981[25]	21	–	10	20	0	–	–	–
Tryzelaar	1982[26]	13	59·7	7·7	15	0	31	–	–
Orringer	1984[8]	100	62	6	–	0	84	17	3
Finley	1985[27]	34	67	2·9	35	1	91	36	2
Baker	1986[28]	20	63	0	–	0	90	25	3
Stewart	1985[29]	21	60	4	52	1	86	–	–
Mahoney	1987[30]	37	62	8	11	0	89	–	–
Shahian	1986[31]	30	62·4	13·3	21·4	2	67	23	5
McInnes	1987[32]	44	71·5	7·5	50	0	73	13	3
Terz	1987[33]	36	57	8	35	3	–	19	3
Hankins	1987[12]	26	58	4	24	1	81	46	2
Barbier	1988[13]	50	65	2	42	1	78	23	3
Current series	1989	54	69	11	41	0	94	10	3

* Orringer, no serious haemorrhage in 200 cases, 47 of them middle-third lesions[11,41]

mobilization and vigorous physiotherapy, and we now consider this technique to be an integral part of the overall procedure.

Inadvertent tearing of the mediastinal pleura accounts for the high incidence of pneumothorax following the transhiatal procedure (63 per cent requiring drainage in Orringer's experience[8]). Likewise fluid collections within the chest cavity are frequent and can be difficult to drain once loculated. In an attempt to minimize these sequelae, bilateral chest drains have been routinely inserted during recent years.

Traction injury to the recurrent laryngeal nerve is an established complication of transhiatal oesophagectomy[8], and we had six (11 per cent) such cases. Acute postoperative stridor required tracheostomy in one patient. The injury is particularly dangerous when combined with a delay in gastric emptying in the early postoperative period, since regurgitation may cause severe aspiration and pneumonia. Recurrent laryngeal nerve injury may also cause cricopharyngeal discoordination, manifested as difficulty with swallowing and laryngeal aspiration[8]. These patients seem particularly susceptible to aspiration of liquids during swallowing, but may tolerate a solid diet. The incidence of recurrent nerve injury can be minimized by early identification and protection of the nerve during mobilization of the cervical oesophagus[8,32], and this complication has been eliminated during the latter part of the series. All but one of the patients who suffered injury to the nerve had resolution of their symptoms, though one is still hoarse.

There were two clinical anastomotic leaks, which presented as temporary salivary fistulae. Both patients manifested their leaks before the 7-day radiological contrast study was performed, suggesting that this investigation may be superfluous, as Wong *et al.* have proposed[34]. Each fistula closed spontaneously and did not give rise to mediastinal sepsis, which is the inevitable consequence of an intrathoracic leak[35]. In each case nutrition was maintained via the feeding jejunostomy, and the patients tolerated the early introduction of solid food in preference to a fluid diet. A feeding jejunostomy is a useful adjunct to the procedure and is recommended in all patients, as it allows early supplementation of calories and frees the patient from cumbersome intravenous lines.

The high incidence of late stricturing at the anastomosis (23 per cent) seen in this series is similar to that reported by others[8,32]. This complication is not confined to the transhiatal approach, of course, and can occur in up to 30 per cent of patients following transthoracic oesophagectomy[21,36], although the stricture rate is generally low[16]. Since gastro-oesophageal reflux is much less with subtotal than partial oesophagectomy, i.e. with an anastomosis in the neck[37], it may be that local ischaemia rather than oesophagitis is responsible for stricture after the transhiatal procedure. All but one of these patients has resumed normal swallowing following a median of three outpatient dilatations, one patient still requiring periodic bougienage. These strictures generally yield easily to the passage of the dilator, suggesting that cricopharyngeal motor dysfunction may play some part in the dysphagia that some of these patients experience[11].

Cervical oesophagogastrostomy after abdominocervical oesophagectomy confers several advantages. The anastomosis is relatively superficial and therefore technically easier to perform than it is within the chest; as stated above, the incidence of symptomatic gastro-oesophageal reflux is much lower (23 *versus* 93 per cent)[35,37]. Subtotal oesophagectomy may be preferable to partial oesophagectomy to minimize the incidence of anastomotic recurrence. The length of the proximal resection margin in oesophageal carcinoma is inversely related to the incidence of anastomotic recurrence[38], and extensive submucosal infiltration of squamous carcinoma[37,39] accounts for the discovery of residual tumour at the proximal resection margin in up to 25 per cent of specimens after partial oesophagectomy[1]. No tumour was found at the resection margins in any of the excised specimens in this series, and the one patient with anastomotic recurrence had an upper-third oesophageal carcinoma.

Surprisingly, exsanguinating haemorrhage has not been a problem in this or other reported series of transhiatal resection (*Table 2*). The median transfusion requirement of 2·5 units of blood seems acceptable, and no patient required an emergency thoracotomy. That massive bleeding is rare (1·5 per cent) with this procedure is perhaps explained by the nature of the vascular supply to the oesophagus. Cast and corrosion techniques in cadavers show that the main feeding arteries divide at some distance from the oesophageal wall[40], so that their small perioesophageal branches may be expected to retract when torn. When it does occur, major bleeding usually results from tearing of the azygos vein invaded by tumour[27,33], suggesting the need to abandon the 'blind' approach for large fixed lesions of the middle third[41]. Interestingly, the incidence of reoperation or thoracotomy for bleeding is much the same with either the transhiatal approach (1·5 per cent) or transthoracic resection (2 per cent)[21]. Nevertheless, transhiatal oesophagectomy is most hazardous for middle-third tumours, where damage to the membranous trachea, main bronchi or thoracic duct has been encountered[42]. For this reason Wong considers that a transhiatal approach for middle-third oesophageal carcinoma is relatively contraindicated[42].

Although the 1-year survival rate was 43 per cent, only

10 per cent of patients have so far survived 3 years. These figures are consistent with the general finding that long-term survival is seldom feasible in this disease[7,43]. Abdominocervical oesophagectomy has been criticized on the grounds that it infringes the principles of 'radical' curative cancer surgery[5]. Yet the proximity of vital organs precludes a satisfactory *en bloc* resection of the oesophagus, even if the incidence of transmural spread (91 per cent) and lymph node metastasis (80 per cent) makes radical clearance theoretically desirable. Generally only the minority of lesions that are confined to the oesophagus are compatible with long-term survival[43], the presence of lymph node metastases reducing the 5-year survival rate by as much as two-thirds[21,44]. Perhaps for this reason, the 3-year survival rate of 17 per cent following transhiatal oesophagectomy[8] is no different from the 14 per cent figure seen after radical *en bloc* excision by conventional oesophagectomy[5] for mid-oesophageal lesions. A better survival rate in Skinner's series[5] ought to have been expected owing to the more favourable pathological staging in his patients (at least 34 per cent stage I or II) compared with those of Orringer[8] (only 16 per cent stage I/II). Similar survival figures to those of Orringer and Skinner have emerged with wider use of the abdominocervical approach in other centres (*Table 2*) and support our contention that this operation does not adversely influence the chance of cure. Ten per cent of our own patients have so far survived 3 years, and this figure may be expected to improve because the median follow-up of current survivors is only 16 months. Nevertheless, whether the current cure rates of 7–22 per cent achieved with transthoracic resection[3,6,21,43] are maintained by employing the abdominocervical approach is unknown, as few studies yet report 5-year follow-up rates (*Table 2*). With the limited clearance margins possible in transhiatal oesophagectomy, we have taken particular interest in the incidence of local recurrence. Although 23 (70 per cent) of those who died had evidence of local recurrence, most of them (85 per cent) died from distant metastases.

In conclusion, abdominocervical oesophagectomy for oesophageal cancer carries morbidity and mortality rates that are at least as low as those seen after conventional oesophagectomy. In our experience it has been applicable to some patients who may otherwise have been refused thoracotomy on the basis of age or general infirmity. The median postoperative survival of 14 months has provided a good quality of life without an apparent increase in the risk of death from recurrent carcinoma. It is therefore a useful palliative procedure which can be safely adopted by surgical gastroenterologists who have an interest in oesophageal surgery. The place of the operation as a curative procedure for carcinoma of the oesophagus is yet to be fully established and awaits longer-term follow-up results.

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Case report

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Purtscher's retinopathy in acute pancreatitis

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The features of pancreatitis affect many systems; eye signs are frequently missed due to ignorance, but their importance lies in the effect of pancreatitis on the capillary bed.

Case history

A 35-year-old man was admitted with acute alcoholic pancreatitis (epigastric pain, vomiting, serum amylase 3945 units/l [normal range <300]). His recovery was marked by symptoms of alcohol withdrawal and the development of a pseudocyst which resolved spontaneously. On the third day after admission he complained of poor vision, describing brown rings obscuring the centre of his visual field. Fundoscopy demonstrated retinal oedema, cotton wool spots, and flame shaped haemorrhages, more severe in the right eye than the left (*Figure 1*). These were felt to be typical of Purtscher's retinopathy. He was re-admitted 8 months later with a further attack of acute alcoholic pancreatitis. On this occasion he denied visual symptoms and fundoscopy demonstrated complete resolution of his previous retinopathy apart from disc pallor.

Discussion

Purtscher's retinopathy was first described in 1910 in a patient suffering a severe head injury[1]. Similar fundoscopic appearances have subsequently been described in patients suffering both major and minor trauma to other systems, after extensive burns, chronic osteomyelitis, ligation of the common carotid artery, and even complicating carotid arteriography and lymphangiography[2]. Inkeles first reported Purtscher's retinopathy in association with acute pancreatitis in 1975[3].

The characteristic fundoscopic appearances are usually found in the area between the macula and optic disc and consist of discrete areas of retinal pallor, fluffy cotton wool spots and flame shaped haemorrhages. The pale areas represent retinal oedema and the cotton wool spots areas of nerve fibre layer infarction. After 4–6 weeks these patches tend to resolve and the fundus may return to a normal appearance, although often there is residual mottling, pigmentary migration and optic atrophy. The appearance of Purtscher's retinopathy is quite distinct from other retinopathies which may occur in a patient with acute alcoholic pancreatitis. These include malignant hypertension, where papilloedema, arteriovenous nipping, and retinal vessel tortuosity are prominent, and the retinopathy of a bleeding diathesis or scurvy where only occasional retinal haemorrhages occur scattered throughout the fundus and with little in the way of cotton wool spots or retinal oedema.

The appearances of Purtscher's retinopathy are believed to be due to ischaemic episodes particularly in the end arteriolar retinal circulation around the macula and disc. Vascular spasm, emboli of fat, air or granulocyte aggregates, and vessel wall damage due to raised intraocular vascular pressure have all been thought to cause the ischaemic episodes[2–4]. Fat emboli or complement-induced leukoembolization are the most favoured explanations for Purtscher's retinopathy in acute pancreatitis[3,5] and similar fundoscopic appearances have certainly been produced experimentally by the injection of glass emboli into carotid arteries[6]. The presenting symptoms vary from a central, paracentral or annular scotoma to large segmental field defects. No treatment is required and there is usually a complete resolution of symptoms. Occasionally if optic atrophy has occurred vision may be permanently damaged.

The frequency of Purtscher's retinopathy in acute pancreatitis is unknown, as the presenting symptoms are often overlooked, either through ignorance or they are submerged by other overwhelming systemic symptoms.

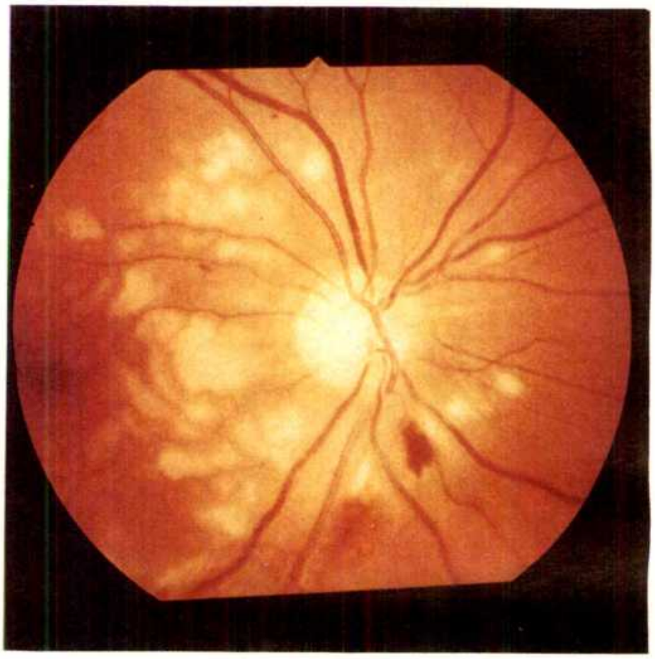

Figure 1 *Right fundus showing typical appearance of Purtscher's retinopathy*

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Short note

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Antabuse® implants: a useful surgical procedure

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Antabuse® (disulfiram) (C.P. Pharmaceuticals, Wrexham, Clwyd, UK) has been prescribed as a deterrent against alcohol abuse for many years[1]. The adverse effects it produces, in the presence of alcohol, were discovered accidentally by two Dutch physicians[2]. They were taking the drug during experiments to investigate its anthelminthic properties and became severely ill at a cocktail party.

It is now well established that disulfiram blocks the metabolism of acetaldehyde, a breakdown product of alcohol, and that this is responsible for a series of symptoms and signs known as the 'acetaldehyde syndrome'[3]. The features of the disulfiram–ethanol reaction include headache, flushing, malaise, dyspnoea, palpitations, vomiting, hypotension and tachycardia. Cardiovascular collapse can occur in severe reactions and deaths have occurred. Antabuse is normally prescribed in the oral form, but some patients are considered more suitable for an Antabuse implant.

Patients and methods

We have performed 49 implantations on 14 patients, 10 men and four women. The age range was 26–53 years with a mean age of 40 years. Three patients had one implant, five had two implants, three had three implants, one had four implants, one had six implants, and one patient had 17 implants. Thirteen of the operations were performed under local anaesthesia and 36 under general anaesthesia.

Transverse incisions were made in the skin of the anterior abdominal wall and in the anterior rectus sheath. Ten sterile Antabuse tablets were placed behind the rectus abdominis. The anterior rectus sheath was closed with continuous Vicryl® (Ethicon, Edinburgh, UK) and the skin was closed with interrupted sutures.

Twelve of the patients have been contacted and the sites of the Antabuse implantations examined. The other two patients have since died; one patient committed suicide and the other died from a cerebral tumour. Both of these patients died several years after their last Antabuse implantation, with no record of any problem relating to the sites of the implantations.

A history of a purulent discharge from the wound was taken to be a significant wound infection.

Results

Of the 49 implantations, 40 (82 per cent) were without complications. There were eight early complications: six wound infections and two occasions when the tablets extruded without evidence of infection. Of the six wound infections, four of the implantations had been performed under general anaesthesia and two under local anaesthesia. In the cases where extrusion occurred, one implantation had been carried out under general anaesthesia and the other under local anaesthesia. There was no relationship between the site of the incision (above or below the umbilicus) and the subsequent development of a wound infection. There was only one late surgical complication; a patient developed a painful scar.

In our series, no serious complication resulting from alcohol intake in the presence of an Antabuse implant occurred.

Discussion

A major difficulty with oral deterrents against drinking alcohol is that of achieving compliance. Antabuse implantation is an attempt to overcome the problem of compliance. Patients referred for Antabuse implantation are motivated to overcome their alcohol problems; they have had some success in the past with oral Antabuse but have found it 'all too easy' to stop taking the tablets and resume alcohol consumption. Of the 14 patients, three still have regular implantations every 6–12 months and they remain abstinent. Five patients are not drinking but are receiving other forms of treatment. Four patients have failed to stop drinking despite Antabuse implantation and two patients have since died. Both deaths occurred several years after implantation and were unrelated to Antabuse implantation. We do not know if these two patients were abstinent when they died.

In the psychiatric literature there are several reports of experience with Antabuse implantation[4–13]. Most authors conclude that periods of abstinence following implantation were significantly longer than those achieved with other forms of treatment in the 2 years before Antabuse implantation. The same authors all used Antabuse implantation in combination with other methods of treatment.

Blood levels of disulfiram can be measured and it has been demonstrated that levels above 0·1 mg/dl are required to produce a disulfiram–ethanol reaction[9]. Blood levels of disulfiram have been measured in patients following Antabuse implantation[9] and the levels were high enough actually to produce a reaction in only a few patients. It was concluded that disulfiram implantation is unlikely to have a prolonged pharmacological effect. It has not been our practice to measure disulfiram levels. It would seem that long-term abstinence attributed to the presence of an Antabuse implant is most likely to be due to a placebo effect.

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Surgery in the undergraduate curriculum – a statement by the Association of Professors of Surgery

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This is our second document produced on academic matters related to surgical practice. Our first publication discussed the place of research in postgraduate surgical training[1]. In this second paper we wish to discuss the present position of surgery in the undergraduate curriculum and whether changes in clinical practice and modifications in educational philosophy might necessitate alterations in emphasis during the clinical years.

Background

Traditionally 'surgery' has maintained a high profile in all medical school curricula although in recent years there has been a diminution in emphasis on the surgical specialties. It should be noted that 'surgical' teaching really means the performance and interpretation of clinical method and management in patients on surgical wards. We teach basic clinical methods on patients who require surgical rather than medical treatment. It should be emphasized that we do not attempt to teach surgical craft or operative technique and that we try to avoid surgical dogma and bombast.

In order to achieve these aims most medical schools include general surgical attachments in the third year to emphasize basic clinical skills, followed by a fourth year in which the surgical specialties are included. In the fifth year smaller 'firms' are designed to provide more intensive and advanced tuition with increasing emphasis on acquiring higher skills and appreciation of management decisions. There is great benefit in part of this training (usually in the fifth year) being undertaken in district general hospitals.

Table 1 shows the median time for attachments in each of the surgical specialties for UK medical schools. Within the general surgical attachment most schools include a series of seminars or topic teaching (usually in the third year) but the emphasis is always on bedside dedicated teaching, out-patient tuition and informal discussion.

Importance of surgery in the curriculum

Surgical patients have always provided a rich harvest of symptoms and signs to which students can apply their basic scientific knowledge, and as a result of which observe living pathophysiology and the often rapid changes that can be produced by appropriate (and sometimes inappropriate) intervention. These personal observations by the medical student make the course exciting and gratifying. In addition basic practical aspects of clinical management can be demonstrated and taught. These include hands-on experience with venepuncture, the setting up of intravenous infusions and central venous catheter insertion, urinary catheterization, learning the principles of sterile techniques in the operating theatre, closing wounds and placing sutures, observing wound healing and breakdown, and the value of appropriate treatment.

Surgical attachments are an essential part of the undergraduate curriculum because of the unique nature of surgery which allows students to be taught:

(a) To become skilled in and to learn the importance of careful history-taking, appreciating in the surgical patient how such care will often aid correct diagnosis in the urgent and emergency situation.

(b) To become skilled in eliciting and interpreting physical signs which can indicate urgent life-threatening conditions and to learn to separate these from more chronic, less urgent, situations.

(c) To learn the appropriate use of investigations, especially interventional investigations. This includes particularly the various uses of endoscopy in both general surgery and the surgical specialties.

(d) To appreciate the importance and need for careful, accurate and speedy decision-making.

(e) To become familiar with the spectrum of surgical care available and to develop a critical attitude to assessing its value in relation to less invasive forms of treatment. This often involves collaboration with colleagues in other disciplines, e.g. gastroenterology, neurology and rheumatology.

(f) To observe and become involved with the management of surgical emergencies, especially in life-threatening conditions resulting from trauma, major haemorrhage, acute sepsis, vascular, respiratory and alimentary obstruction.

(g) To understand and be involved with the management of acutely critically ill patients, especially in relation to cardiorespiratory support, circulatory support, fluid and electrolyte balance and pain relief.

Table 1 *Surgery in the curriculum*

	Median no. of weeks (range)	Percentage of medical schools
General surgery (with urology teaching)	22 (13–28)	100
Orthopaedics	5 (2–8)	100
Ear, nose and throat	2 (1–6)	100
Ophthalmology	2 (1–4)	100
Neurosurgery/neurology	2 (1–6)	64
Cardiothoracic	1	32

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(h) To acquire communication skills, particularly with anxious and depressed patients and to explain in simple lay terms complex procedures which are indicated or which have been carried out. This involves experience in the counselling of patients and relatives.

(i) To supplement teaching on anaesthesia and to apply the pharmacology of various drugs including analgesics.

(j) To emphasize the important ethical, moral and social issues involved in surgical practice and to introduce discussions on cost–benefit analysis.

(k) To appreciate the appearance of normal and abnormal tissues in the operating theatre.

(l) To develop a healthy critical faculty.

Recommendations

Members of the Association of Professors of Surgery are aware of a range of difficulties which surgical teachers face in common with other clinical teachers in providing a comprehensive and wide-ranging clinical teaching programme along conventional lines.

In recognizing these problems, but nevertheless being aware of the importance of surgery in the undergraduate curriculum, the Association has discussed a number of possibilities which might more effectively utilize the time available within undergraduate curricula for surgical attachments.

These suggestions are designed merely as 'bare-bone' guidelines which should be taken into consideration by medical schools, the University Funding Committee and General Medical Council, and ultimately curriculum committees as mechanisms for enhancing undergraduate training:

(1) A clear statement of the objectives of surgical attachments should be available to all students in their first clinical year.

(2) A generally agreed 'core curriculum' including surgical principles should be agreed by boards of surgical studies and emphasized throughout the third year teaching.

(3) Surgical attachments should include specialty exposure allowing principles of management to be exemplified by observing treatment of specific organ abnormalities.

(4) Out-patient teaching should be enhanced. This will necessitate better facilities for teaching in out-patient departments, and patient numbers should be limited to enable teaching to occur in a calm and unhurried atmosphere.

(5) Arrangements should be made to enable students to be taught on patients attending for day case surgery. This would require careful organization of lists ahead of admissions.

(6) Students should be encouraged to comment on the teaching expertise and enthusiasm of each firm and note taken of comments on poor teachers. The consumers' views should be taken into account. Equally a formal clinical assessment should be conducted at the end of each teaching attachment or curriculum block to identify accuracy in clinical skills.

(7) It is important that assessment of surgical teaching should be used to determine selectivity and funding in addition to research output.

(8) National Health Service (NHS) consultants involved in teaching undergraduates should have this recognized clearly within their contracts. In addition to out-patient teaching, teaching on business ward rounds and during operating lists, the Association feels that a minimum of 2 h of dedicated bedside teaching per week is necessary by NHS consultants involved with undergraduate teaching.

(9) If the 'knock-for-knock' arrangement between medical schools and the NHS is phased out, the Association supports the idea of Service Increment for Teaching funding 'following the student' so that units which have developed a strong commitment and enthusiasm for teaching will be suitably rewarded.

(10) Specific tuition in trauma and in the care of the critically ill should be included in the curriculum, probably during the surgical attachments.

(11) Clinical curriculum subcommittees should allow a degree of flexibility to enhance the contribution that surgery can make to undergraduate training. This will inevitably mean taking account of the rapidly changing practices of surgery. In addition consideration should be given to enable students to study a subject-in-depth for a period of up to 6 months. Surgery and its specialties afford many such excellent opportunities.

Conclusions

The wide range of experience that can be gained in eliciting and interpreting clinical symptoms and signs, as well as in learning the value of management and decision-making, ensure that surgery attachments must form some of the most important components of all medical school clinical curricula. Nevertheless changes in surgical practice have meant that in order to ensure that students continue to benefit from these attachments and obtain the necessary exposure and training, various alterations in work patterns are necessary. The Association of Professors of Surgery hopes that by recognizing the problems and providing recommendations for updating surgical teaching, 'surgery' will continue to maintain its high profile in the undergraduate curriculum.

Acknowledgements

This paper condenses the views expressed in two debates by the Association of Professors of Surgery. Many professors contributed but we are particularly grateful to Professor M. Baum and Professor K. Hobbs.

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Evolution of catgut ligatures: the endeavours and success of Joseph Lister and William Macewen

And they sewed fig leaves together and made themselves aprons. Genesis 3:7.

It must have been a great convenience to Adam and Eve to have their 'aprons' made of biodegradable material which would reliably disintegrate after a short and regular time interval. It would have been equally, if differently, convenient for the early pre-Listerian surgeons to have a similar material for the subcutaneous ligatures which were needed for amputations, obliteration of major blood vessels to cure aneurysms, or closing the 'ring' in hernia repairs.

Force was required in tying such ligatures which had to be strong. It was recommended, for example, that the inner and middle coats of major arteries should be ruptured to promote thrombosis when pulling the ligature tight. Silk, twine, horsehair and silver wire were some of the materials used. One or both ends of the knot were left long enough to protrude from the wound, partly for drainage, partly for ease of removal. But they also provided a route for infection to enter the depths of the wound and sepsis, pyaemia and secondary haemorrhage were common. What was required was a strong flexible material which could be easily knotted, would remain intact in the tissues until its purpose had been fulfilled and then be completely absorbed or at least made inactive, and be able to be buried totally subcutaneously with no knot ends trailing to the surface. The two surgeons (perhaps the greatest of their era) who solved the problem were Lister and Macewen.

Lister came to Glasgow in 1860 as Regius Professor of Surgery in the University. In 1865, he began the antiseptic era by treating a compound fracture of the lower leg in 11-year-old James Greenlees with carbolic acid and achieving complete healing without infection. Soon afterwards he began his experiments on improving ligature material. He left for Edinburgh in 1869 and subsequently went to London.

Macewen was 21 years younger than Lister and did not graduate in Glasgow until 1870. As a student he must have attended Lister's lectures and ward rounds and he became a firm believer in antisepsis and carbolic acid. Later he was to use asepsis in place of and in addition to some antiseptic techniques. In 1892, he applied for and obtained the post of Regius Professor of Surgery at Glasgow University, and Lister supplied one of his 'testimonials'.

In the *British Medical Journal* of 1881 there appeared in the issue of 29 January a paper by William Macewen entitled 'Clinical lectures on some points connected with the treatment of wounds. Lecture 1. Ligature'. By an extraordinary coincidence the issue of the following week (5 February, 1881) contained the first part of Joseph Lister's Presidential Address to the Clinical Society of London, 'On the catgut ligature'. The second part of his address was published one week later. It is remarkable that the two surgeons who were responsible for the successful development of catgut ligatures should have their observations published within 2 weeks in the same journal. Lister's paper is longer and more detailed than Macewen's and of course they were written for different readerships. To begin with, they covered much the same ground although occasionally Macewen adds a detail which Lister has omitted. In the end they come to similar conclusions, but there is no doubt that Lister's product was superior to Macewen's. Lister, however, had started his experiments with ligatures while Macewen was still a medical student and, to begin with at least, Macewen had simply followed his master's lead.

With his continuing success with carbolic acid and the antiseptic method of wound healing, it must have seemed to Lister that, if he were to sterilize the material then in use with carbolic acid, a permanently buried ligature might be achieved. It would not be absorbed but might remain inert as some bullets and other foreign bodies occasionally did. He chose silk because its smooth surface made it unlikely to cause physical irritation in the tissues. At first he had some success (see *Lancet* 1869: 451) but he and others had later problems. At best the silk ligature would be encapsulated with fibrous tissue but this was unusual; more often, sooner or later, it was extruded or had to be removed because of pus formation.

There was, however, another strong flexible material, catgut, which had attracted some surgeons but had given disappointing results. When, in the dry state, it was imbedded in the tissues it rapidly absorbed fluid and within 24 h or so it had become soft, pulpy and the knot no longer held. Yet it had many advantages. It was readily available and used, among other things, to string a variety of musical instruments because of its resistance to large breaking strains and its relative lack of stretching when under tension. It was cheap; a gross of hanks (i.e. skeins) cost 12 pence (perhaps £4 or so today) and a single hank cost 1 penny. It seemed to have everything required of a ligature except for the excessive rapidity of its absorption. If this process could be slowed down to an acceptable 2–3 weeks, a useful ligature material would have been found.

Lister visited a catgut manufacturer and was impressed not only by the crudity of catgut preparation but by the beauty of the final product. He is worth quoting:

> Catgut, as you are all doubtless aware, is prepared from the small intestine of the sheep. The gut is treated in what seems an exceedingly rude manner for so delicate a structure. It is scraped with some blunt instrument, such as the back of a knife over a board; and by this means, as the people express it, the dirt is scraped out. That which these people call dirt is the exquisite and complicated structure of the intestinal mucous membrane. But, while the mucous membrane is scraped out from within, there is also scraped off from without the circular coat of muscular fibres. The result comes to be that the intestine is converted into a comparatively insubstantial material; this exquisitely delicate structure from which the catgut is prepared is neither more nor less than the sub-mucous cellular coat of the intestine .... I was astonished to find that, after this scraping process, the intestine could be blown up still as a continuous tube.

For the thickest form of catgut, the complete tube was attached to a wheel, twisted until tight and then allowed to dry. For the finer kinds, the tube was slit up from inside by a number of razor blades set in a conical piece of wood. Usually the fresh catgut was exposed to the fumes of burning sulphur or bleached by potash. But Lister thought the latter were

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unnecessary; it was the twisting and drying that were essential.

Lister used a wide variety of carbolic acid solutions to find out if, thereby, he could retard the absorption process. He could, but the initial preparation took a very long time; 2 months was a minimum, 6 months much better and a year best of all. But this raised problems; a supplier, who had run out of 6 months' stored catgut, was likely to replace it with relatively fresh material causing disastrous clinical results. Lister showed little respect for his suppliers and recommended that the surgeon should make and keep his own ligatures.

He began to suspect that this long period of delay, which was necessary before use, was an inherent property of the catgut and unrelated to his antiseptic solutions. This was confirmed one wet Christmas day when he met an old fiddler going into the Royal Infirmary in Edinburgh to entertain the patients. But the fiddler said that his fiddle would not work properly that day since the wet catgut strings had not been properly seasoned. That catgut could be 'seasoned' in the same sense that wood is seasoned was a new concept to Lister, who realized that some of his early successes with carbolicized gut probably resulted from his use of old well-seasoned gut.

The problem now was to try to shorten this seasoning process and for suitable materials he turned to the leather industry. 'One substance that suggested itself was tannic acid so as to convert the fibrous tissue of the catgut into leather.' He had some success but in one respect tannic acid was a failure. 'I have not obtained by means of tannic acid a kind of catgut that is not too speedily absorbed.' The next substance he used was chromic acid on 'account of its well known effect in hardening tissues'. By itself chromic acid did not work very well but, when mixed with other substances, particularly glycerine, the results proved more hopeful.

Macewen, in 1881, reported that he had been experimenting with catgut prepared in chromic acid and glycerine for some years. A watery solution of chromic acid, one part to five, was added to glycerine in the proportion of one part to two. The hanks of catgut were inserted in this solution and retained there for 7–8 months before being stored in a solution of carbolic acid and glycerine (one to ten) until ready for use. The ligatures were strong and persisted for 2–3 weeks, long enough for clinical purposes. 'Mr. Lister' he writes 'has been endeavouring to secure a ligature and believes he has now succeeded; but hitherto he has not seen fit to publish his results.'

Lister had 'not seen fit to publish his results' because he wanted to take the method of preparation one stage further and avoid the delay of 7–8 months before use. In his paper of 1881 he announced success and told the Clinical Society of London how it was done. 'I dissolve one part of chromic acid in 4000 parts of distilled water and add to the solution 200 parts of carbolic acid; ... minute as is the quantity of the chromic acid, it exerts, when in conjunction with carbolic acid, a most powerful effect upon the gut.' If the solution was left by itself, some colour changes occurred within a few hours and a reddish grey precipitate formed. If, however, catgut about equal in weight to the carbolic acid was added as soon as the ingredients were mixed, there was little change in colour and no obvious precipitate which was presumed to have been deposited in the catgut. After 48 h the effect of the chromic acid appeared to be complete and the catgut could be removed from the solution, dried and stored in one in five carbolic oil ready for use. Lister tested its rate of absorption firstly by incubation in warm blood serum obtained from the slaughterhouse and secondly from clinical use. He came to the conclusion that 2–3 weeks would pass before 'erosion' and absorption of the ligature would occur.

MacEwen's method worked but the delay of 7–8 months in preparation was a nuisance. Lister had overcome this and produced ligatures that required only a few days preparation while still retaining their delayed rate of absorption. Lister went on trying to improve his catgut ligatures for many years and manufacturers have developed other techniques but the above method, which Lister published in 1881, was really the end of the beginning.

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The role of interventional radiology for complications of cholecystectomy

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This report summarizes diagnostic and therapeutic radiologic procedures in 45 patients who suffered major complications from cholecystectomy. Complications were divided into (1) bile duct injury or ligation and (2) a variety of pathologic fluid collections. Specific lesions were bile duct injury (n = 6), accidental bile duct ligation (n = 12), ductal stricture (n = 12), abscess (n = 11), biloma (n = 7), hematoma (n = 5), infected pancreatic pseudocyst (n = 3), and stones (n = 2). Presenting problems were sepsis, jaundice, and intermittent cholangitis. The patients underwent 104 interventional radiologic procedures including 29 percutaneous transhepatic cholangiograms, 21 percutaneous biliary drainages, 12 balloon dilatations of strictures, drainage of 11 abscesses, 8 bilomas, 5 hematomas, and 3 pancreatic pseudocysts. Stones were removed by baskets in 2 patients; 12 pressure and perfusion studies were performed. One hundred of 104 procedures were successful; there was one failed biliary drainage, one unsuccessful stricture dilatation, one unsuccessful hematoma drainage, and one recurrent biloma. Thirty patients were spared another operation. The percutaneous procedures were beneficial although not curative in 14 of 15 patients who underwent reoperation; in those patients the procedures helped to establish a diagnosis, improve the patient's preoperative status, or serve as a landmark for the surgeon to locate and repair the ligated or injured duct. One patient died after reoperation, a 2.2% mortality rate. Sectional imaging studies combined with interventional radiologic procedures help to diagnose promptly and effectively treat major complications of cholecystectomy. These interventional procedures either cure the complication and obviate reoperation or aid the surgeon by relieving sepsis and jaundice before reoperation and providing an intraoperative guide for bile duct reconstruction. (SURGERY 1990;107:632-8.)

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CHOLECYSTECTOMY IS ONE of the most common abdominal operations in the United States. Approximately 500,000 cholecystectomies are performed annually.[1-3] The operation generally is well tolerated, particularly in young and middle-aged patients. Morbidity is reported to be from 4% to 32% in several large surgical series,[1, 3-8] whereas mortality rates vary from 0.4% to 2.5%.[1-6, 8-11] The most frequent complications of cholecystectomy are wound infection, abscess formation, ductal injury or ligation, and bleeding.[3, 12-20] Elderly patients undergoing emergency cholecystectomy are more prone to complications and serious sequelae; their mortality rate is approximately double that of young patients.[1, 5, 6, 9]

During the past 4 years, we have performed interventional radiologic procedures in 45 patients to diagnose and treat serious complications of cholecystectomy. This report describes the spectrum of these procedures and the benefits of interventional radiology for the surgeon in the treatment of these patients.

MATERIAL AND METHODS

The 45 patients who underwent cholecystectomy include 34 women and 11 men whose ages range from 19 to 82 years. Complications were appreciated at the time

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Table I. Interventional radiologic therapy for complications of cholecystectomy (n = 45 patients)

*Complication**	*No. of patients*	*Radiologic management*	*Result (success)*
Abscess	11	PAD	11/11
Other fluid collections			
Biloma	8	PAFD	7/8
Hematoma	5		4/5
Pseudocyst	3		3/3
Ductal transection	6	PBD	5/6
Ductal ligation	12	PBD	12/12†
Ductal stricture	12	Balloon dilatation	11/12
Stones (caused by strictures)	2	Basket removal	2/2

PAD, Percutaneous abscess drainage; *PAFD*, percutaneous abscess/noninfected fluid drainage.
*Several patients had more than one complication.
†Bile duct drained, cholangitis and jaundice relieved; patient operated on for ductal reconstruction.

of surgery in four patients (hepatic injury in three and ductal transection in one). In the remainder of the patients, symptoms or signs became apparent from 2 days to 11 months after cholecystectomy. The majority of these patients were referred to surgeons at our institution; as such, this study yields no prospective information on the incidence of complications. Presenting complaints were right upper quadrant pain (14 patients), fever and chills (35 patients), and jaundice (21 patients) (more than one complaint was present in many patients). Common duct exploration had been performed in 16 patients.

The interventional radiologic procedures included 29 percutaneous transhepatic cholangiograms (PTC), 21 percutaneous biliary drainages (PBD), 12 balloon dilatations of strictures, percutaneous drainage of 11 abscesses, 8 bilomas, 5 hematomas, and 3 pancreatic pseudocysts. The most common indications for PBD were fever, cholangitis, and septicemia. The PBD catheter was useful as an intraoperative landmark in the cases of ligated ducts or ductal injury; lowering of the bilirubin value was not used as an indication for PBD. Percutaneous removal of stones was performed in 2 patients; 12 patients underwent pressure and perfusion studies. These dynamic studies were used to help determine when to remove the PBD catheter after balloon dilatation of strictures; normal study results prompted removal, whereas abnormal study results (elevated pressure, pain, and ductal dilatation) indicated the need for further balloon dilatation.[21] The stones that were removed occurred as a result of postcholecystectomy strictures and were not retained common duct stones. All procedures were performed in the standard fashion with fluoroscopic guidance for bile duct manipulations and ultrasonographic (US) or computed tomographic (CT) guidance for abscess and fluid drainage.

RESULTS

One hundred of 104 procedures offered at least immediate relief of symptoms and signs. Four failed procedures occurred: one was a biloma that recurred; the second was an unsuccessful attempt to cannulate intrahepatic bile ducts in a patient with a mid common duct injury and leakage. The third patient underwent three unsuccessful sessions of balloon dilatation for a common duct stricture (ie, the stricture could not be obliterated by the dilatation balloon; the patient eventually underwent reoperation and choledochoenterostomy). The final patient underwent reoperation for combined ductal reconstruction and hematoma evacuation. Cures were effected in all 11 patients with abscesses (Fig. 1), in 7 of 8 bilomas (1 patient underwent drainage twice), in 4 of 5 patients with hematoma drainages, and in the 3 patients with pancreatic pseudocysts (2 were infected).

In all 29 PTC procedures the bile ducts were cannulated and revealed the following causes: 9 bile duct strictures, 6 injured and leaking common ducts, 2 patients with ductal stones, 7 ligated common or left hepatic ducts, and 5 ligated aberrant right hepatic ducts. Four simultaneous PTCs demonstrated normal nondilated ductal systems apart from the ligated aberrant right hepatic ducts. The 21 biliary drainage procedures permitted relief of both cholangitis and pruritus in patients with jaundice (Fig. 2) and provided access for stone removal and balloon dilatation of strictures. Three strictures were dilated through existing T tube tracts (Fig. 3) and nine through transhepatic tracts. Balloon dilatation of strictures was considered adequate (11/12 cases) when (1) the balloon could be opened and the stricture waist obliterated, (2) the postdilatation dynamic pressure and perfusion fluid challenges caused no bile duct dilatation, rise in pressure, or pain, and (3) the patient was able to tolerate catheter clamping for at least

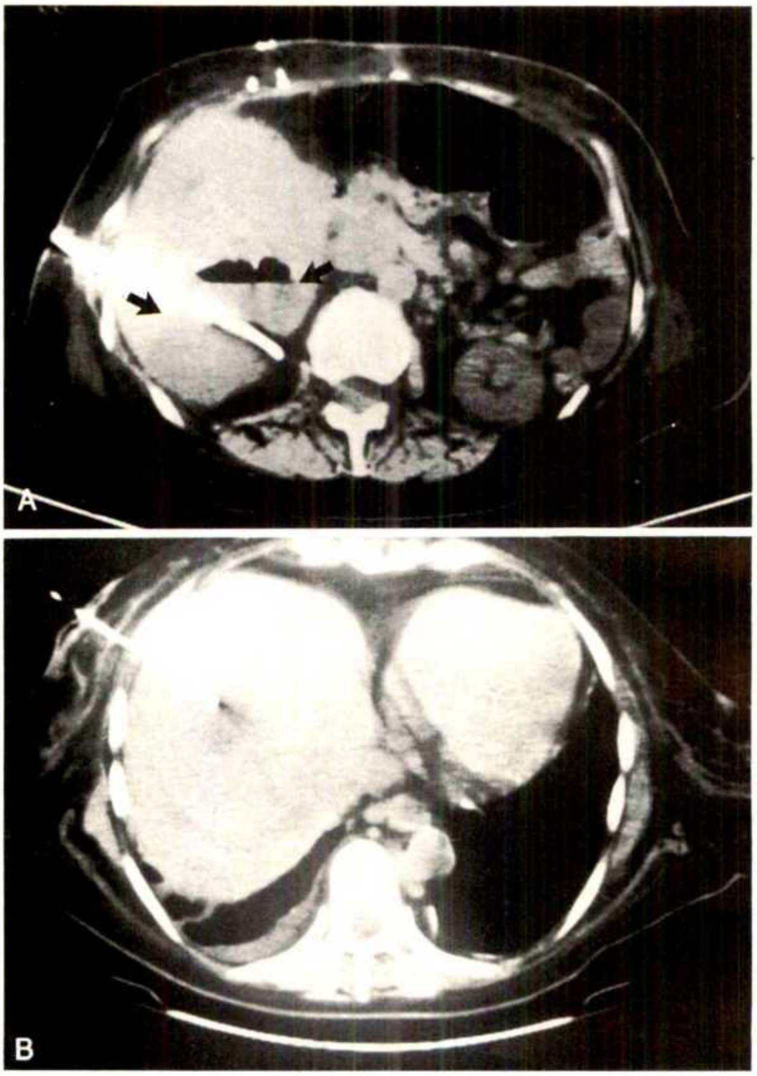

Fig. 1. Successful percutaneous drainage of postcholecystectomy intrahepatic abscesses. This 52-year-old woman had a fever of 102° F and right upper quadrant pain 2 weeks after cholecystectomy. **A,** CT-guided drainage of large abscess *(arrows)* in posterior right hepatic lobe with 12F sump catheter. **B,** Smaller, more cephalad abscess was evacuated by sheath aspiration only. Patient recovered well.

a few days. One elderly patient has had long-term PBD (1 year) for both an injured and a high ligated duct. Repeat operations (n = 15) were performed for reconstructive choledochoenterostomy or hepaticoenterostomy after accidental bile duct ligation (12 patients) (Fig. 4), to bypass an extrahepatic duct stricture (1 patient), for persistent common duct leakage (1 patient), and for combined ductal reconstruction and hematoma evacuation. The latter patient died after reoperation (Table I).

DISCUSSION

Although major complications are uncommon after cholecystectomy, their occurrence may be devastating.[2, 15] Delay in diagnosis of an abscess, a bile collection, or an injured or obstructed bile duct may lead to cholangitis, sepsis, and jaundice; in high-risk, elderly patients or patients after surgery, these complications may prove fatal.[2-5, 9, 17] The mortality rate after cholecystectomy increases with age: 3% to 4% of patients over 60 years of age died in one large series, and the rate rose to more than 13% of patients over 80 years of age in other reports.[4, 5, 9-13] Postcholecystectomy bile duct injuries were lethal in 31% to 36% of patients in several reports.[11, 12, 16-20, 22]

In our series, 30 of 45 patients were spared repeat operation, and one patient died (2.2% mortality). The low mortality rate likely was partly the result of expe-

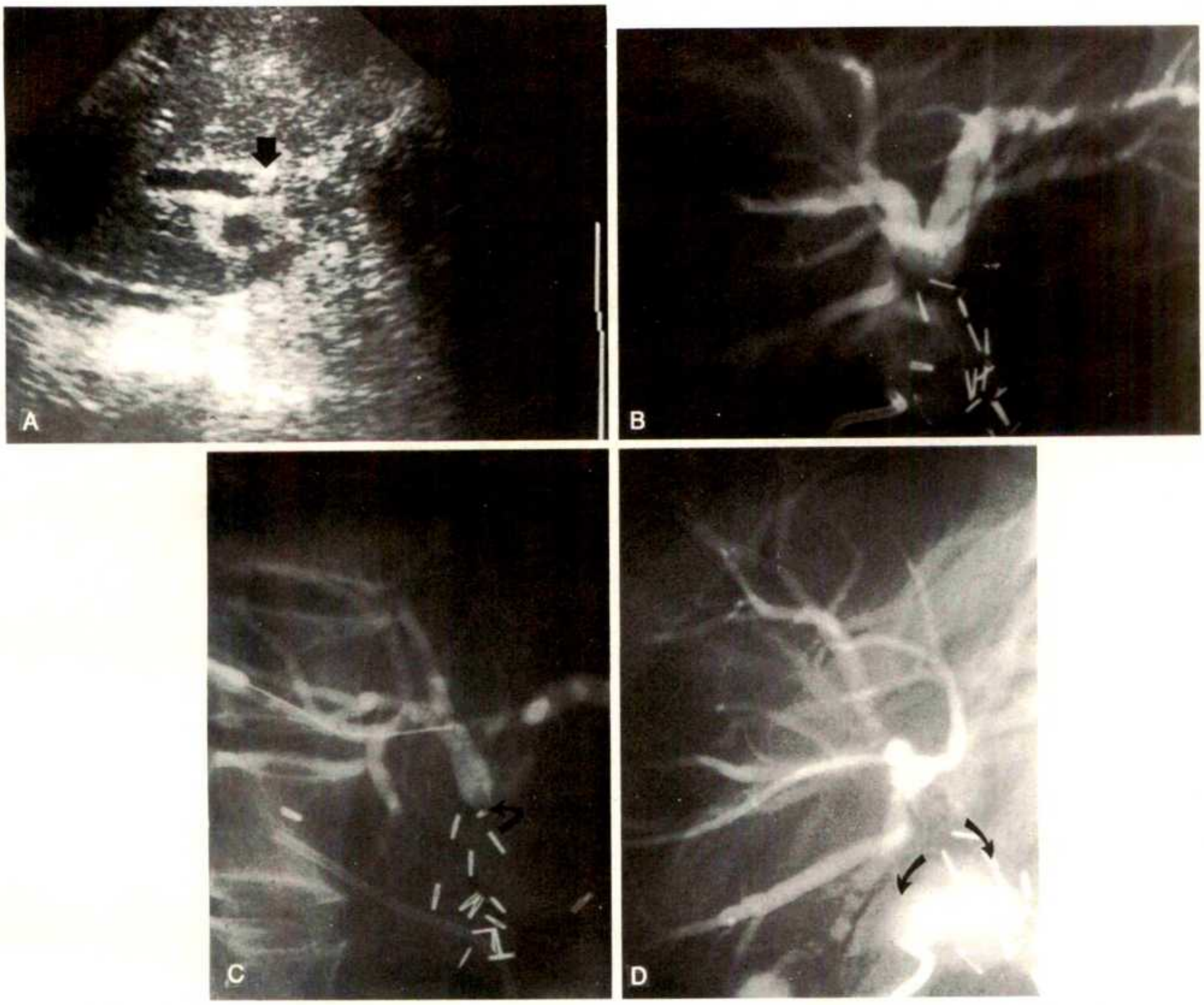

Fig. 2. Percutaneous diagnosis and treatment of accidentally ligated common hepatic duct at cholecystectomy. This 62-year-old man had sepsis and hypotension at the time of PTC and PBD; frank pus was removed from the bile ducts. **A,** US demonstrates dilatation of the main right hepatic duct with an echogenic density with shadowing at the distal portion of the visualized duct *(arrow)*. **B,** Frontal view at PTC demonstrates total obstruction at the level of the confluence. (*Arrow* is on incriminating surgical clip that caused shadowing on sonogram.) **C,** Lateral view during PTC clearly demonstrates the offending clip *(arrow)* on the duct in the 90-degree plane. **D,** PBD relieved the patient's sepsis. The catheter was an essential guide for the surgeon during ductal reconstruction. Note also percutaneous drainage of associated biloma in this patient *(arrows)*.

ditious use of imaging and diagnostic and therapeutic interventional techniques. Those patients who required biliary-enteric reconstruction for ligated and injured bile ducts were improved clinically with respect to cholangitis and sepsis by PBD before reoperation.

A variety of diagnostic and therapeutic radiologic procedures may benefit the complications of cholecystectomy. Diagnostic percutaneous aspiration and therapeutic drainage should cure the majority of abscesses and other fluid collections. Drainages were successful in 25 of 27 (92.9%) patients in this series. The fluid collections were located predominantly in the right upper quadrant (subhepatic, subphrenic, and intrahepatic). Other fluid collections occurred contiguously and even remotely: in the peripancreatic region, the left subphrenic space, and even the left paracolic gutter and left iliopsoas muscle. CT was used to guide drainage in most cases and US in the remainder.

PTC accurately defines the aforementioned biliary complications and provides anatomic delineation of the

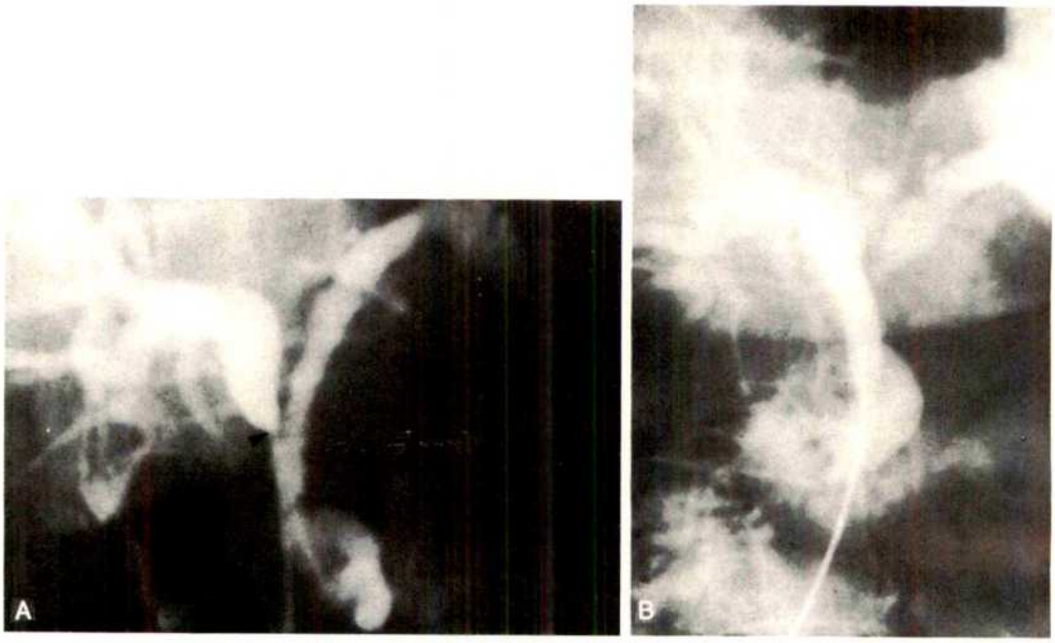

Fig. 3. Percutaneous dilatation of postcholecystectomy ductal stricture. This 72-year-old woman underwent a difficult cholecystectomy with bleeding and possible injury to the duct. A T tube was left in the duct. **A,** One month later, T tube cholangiogram demonstrates a stricture of the right hepatic duct at the confluence *(arrow)*. **B,** The stricture was dilated by a balloon catheter.

injury or obstruction. Nondilated ducts may need to be punctured and opacified in these patients as well. Preliminary US and CT yield pre-PTC clues to the site and cause of duct abnormalities, such as intrahepatic versus extrahepatic obstruction or segmental obstruction caused by an aberrant ligated duct. However, cholangiography offers specificity and further precision often required for operative roadmapping. Although endoscopic retrograde cholangiopancreatography is an alternative to PTC for some cases of obstructive jaundice, it does not provide the equivalent antegrade detail that PTC does; this is particularly so with ligated aberrant right hepatic ducts that are excluded and sequestered from the main bile duct system. Antegrade detail also is important proximal to a ligated common hepatic duct to outline the location and length of extrahepatic duct for choledochojejunostomy.

PBD tracts serve many purposes in these patients: to decompress obstructed ducts in patients with cholangitis, to stent and identify injured ducts, as access for balloon dilatation of strictures, and for basket or occlusion balloon removal of stones (and potentially for stone dissolution). PBD was not used to relieve jaundice per se, because this is not considered essential before surgery. Although stricture dilatation appeared adequate in the short-term, long-term follow-up is needed to appreciate its effect fully.[23] Those patients in whom reoperation was necessary to perform a bypass or who underwent bile duct reconstruction were rendered free of sepsis and were markedly improved by PBD before surgery. In addition, surgeons obtained important intraoperative benefit by these preoperatively placed percutaneous catheters; the catheters aided localization and identification of the proximal segments of ligated and injured ducts during reconstructive surgery. Without a catheter guide in place, identification of these ducts can be frustrating and time-consuming at surgery because of extensive scarring and inflammation that obscure the anatomy.

Those complications of cholecystectomy that are unsuspected are associated with a delay in diagnosis; consequently the prognosis is poorer.[3, 12, 15] When a cholecystectomy is technically difficult, surgeons are more likely to be cognizant of possible complications. Conversely, with so-called "uncomplicated" or "easy" simple cholecystectomies, complications usually are unsuspected. The latter was the rule in most of our patients and likely led to the severely ill status of many patients at presentation.

The diagnosis and management of postcholecystectomy problems is a classic example of the present-day interplay between the abdominal surgeon and the gas-

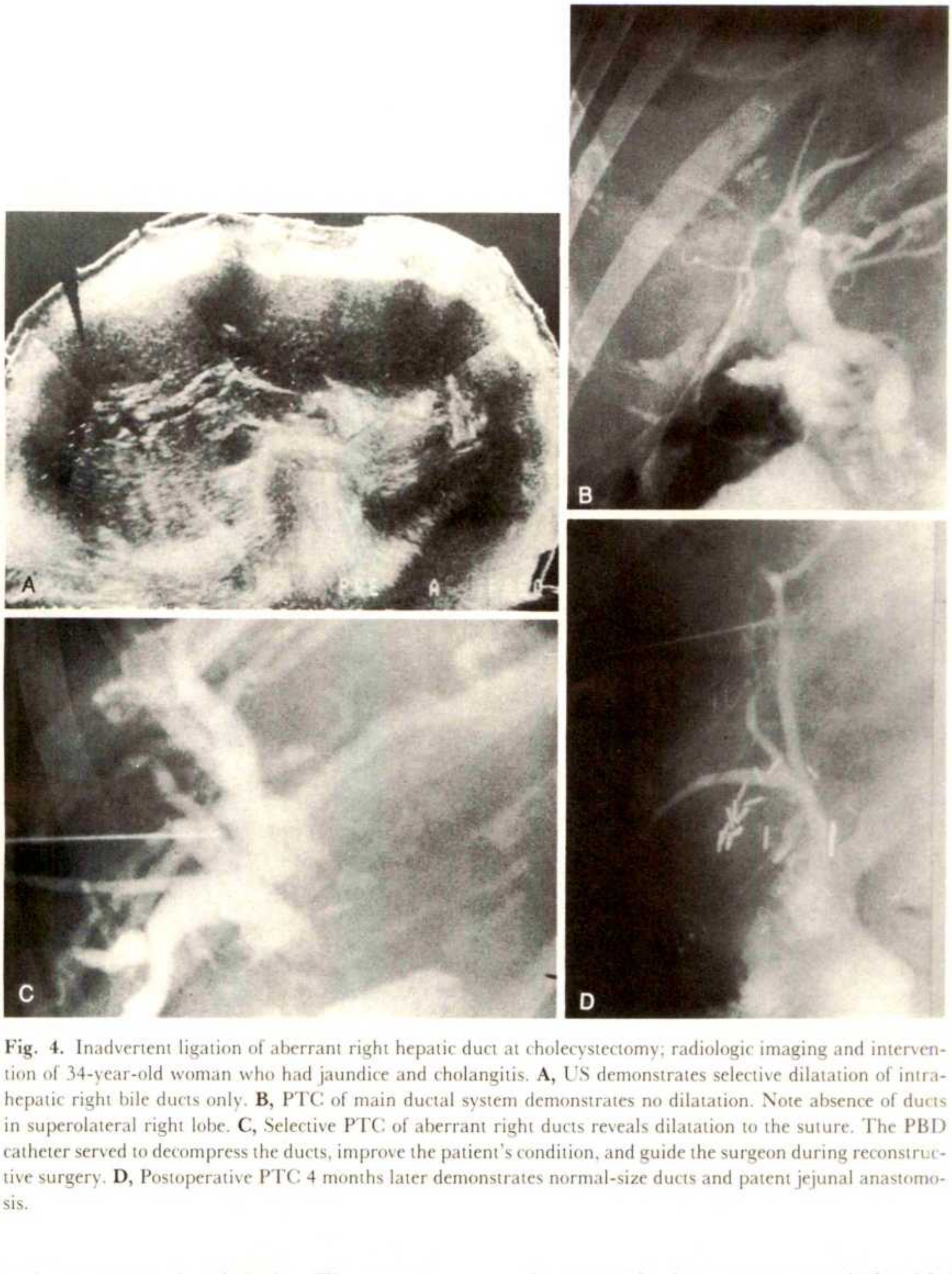

Fig. 4. Inadvertent ligation of aberrant right hepatic duct at cholecystectomy; radiologic imaging and intervention of 34-year-old woman who had jaundice and cholangitis. **A,** US demonstrates selective dilatation of intrahepatic right bile ducts only. **B,** PTC of main ductal system demonstrates no dilatation. Note absence of ducts in superolateral right lobe. **C,** Selective PTC of aberrant right ducts reveals dilatation to the suture. The PBD catheter served to decompress the ducts, improve the patient's condition, and guide the surgeon during reconstructive surgery. **D,** Postoperative PTC 4 months later demonstrates normal-size ducts and patent jejunal anastomosis.

trointestinal interventional radiologist. The surgeon needs to have a high index of suspicion when a postcholecystectomy patient has significant symptoms or signs, and he or she must expeditiously request screening US, CT, or PTC. Similarly, the radiologist should be aware of the potential problems and complications that surgeons may encounter after cholecystectomy; the radiologist must assist the surgeon aggressively with imaging and interventional techniques. The beneficiary in this union between the surgeon and the radiologist is the patient, as evidenced by the low morbidity and mortality rates in this combined approach, despite these severe and potentially lethal complications of cholecystectomy.

Our appreciation goes to Michael Bauman, RT, for technical assistance.

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Correspondence

War wound excision

Sir

Fackler's contribution to the understanding of wound ballistics is acknowledged He has shown that modern rifles do not always cause dramatic wounds. Like many military authors he thinks that rifle wounds are the only wounds worth discussion In an International Committee of the Red Cross (ICRC) hospital the 'great majority' of war wound are not 'punctate through-and-through rifle wounds of the extremity with minimal tissue disruption'. His response (*Br J Surg* 1989, **76**: 1217 (letter)) to the advice on war wound management from the ICRC[1,2] is unacceptable because·

(1) He chooses to ignore the enormous experience of the authors in the continued care of war injured The 'thorough review of historical war surgery experience' clearly missed the reports of others who had responsibility to the patient beyond initial surgery Davis[3] witnessed the evacuation of wounded from Vietnam onto a hospital ship and concluded: 'the mechanism for every failure lay in inadequate debridement of a given wound' Likewise Latta[4] managing wounded from Korea stated. 'It was abundantly evident that nothing yet can take the place of the efficiently planned surgical toilet of the wound'. The mainstay of Trueta's[5] closed plaster technique for limb fractures was careful wound excision It is clear that those concerned with the continued care of the patients rapidly recognize the value of correct wound surgery. A modern army wishing to evacuate the patient rapidly may find it acceptable to teach their forward surgeons time saving but suboptimal wound surgery. In this situation the surgeon cannot gain the valuable feedback necessary to learn wound excision. In an ICRC hospital, surgeons new to war surgery sometimes choose to ignore advice from those with more experience. There is an immediate increase in bed occupancy and number of reoperations. It is incomplete wound excision that, 'imposes an unnecessary drain on surgical resource and inflicts a higher than needed complication and morbidity rate upon the patient'

(2) The experimental work that Fackler *et al.* use to support their argument[6] is not applicable It is only by a long stretch of the imagination that the shooting of ten anaesthetized pigs through the muscular part of their thighs, 'conform as closely as possible to the real-life combat situation' The fact that this has influenced the rewriting of the NATO handbook[7] is very distressing

(3) Fackler takes exception to the excision of wounds that present late. What does he advise for large volumes of dead tissue rendering the patient toxic and anaemic? Loose bone fragments (sometimes from other people), clothing, mud, stones, grass and pieces of shoe cannot be left to discharge themselves from the wound The increased blood loss when operating through inflamed tissues around such wounds is inevitable.

One can only conclude that Fackler has lost sight of the pathology that is produced by armed conflict.

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Modern aids to clinical decision making in the acute abdomen

Letter 1

Sir

All surgeons dealing with the acute abdomen must have been fascinated by Messrs Paterson-Brown and Vipond's exhaustive, and no doubt exhausting, review article (*Br J Surg* 1990; **77**· 13–18) No doubt the computer aided diagnostic and investigative measures they describe will improve accuracy in the diagnosis of the acute abdomen, but the expense and time of them, I am quite sure, can be avoided, particularly in the case of the 'query appendix' by testing for abdominal wall tenderness, which we described in the acute abdomen several years ago[1]. We have found the test of equal use in the elimination of organic disease in patients with chronic obscure abdominal pain (in preparation). Abdominal tenderness is one of the physical signs which most persuades the surgeon to take up the knife, finding that tenderness to be greatly enhanced by tensing the abdominal muscles (when logic suggests the underlying peritoneum and viscera must be protected from distortion) greatly reassures him in the rightness of putting it down again. Of course like all tests it must be interpreted in the perspective of a full history and examination, and that most useful tool, particularly in children, reassessment an hour or two later – and again if necessary It is though costless, quick, and entirely unharmful

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Letter 2

Sir

Paterson-Brown and Vipond have presented an erudite review of modern aids in the assessment of the acute abdomen (*Br J Surg* 1990, **77** 13–18) They state correctly that peritoneal aspiration cytology 'does not differentiate between acute inflammatory conditions requiring surgery and those that do not' and go on to conclude that aspiration cytology is 'more preferable' than diagnostic peritoneal lavage (DPL). I disagree with this conclusion.

Having gone to the trouble of inserting a catheter into the peritoneal cavity, the surgeon can, with very little extra effort or inconvenience, gain additional useful information by performing DPL rather than by merely aspirating for white cells If the lavage fluid is sent for assessment of amylase, bile and bacterial content, it is possible to differentiate some conditions requiring surgery from others which do not

Perforated peptic ulcers, acute pancreatitis and strangulated or infarcted bowel have similar clinical presentations. All three may cause a rise in serum amylase and all three will give a positive aspiration of white cells from the peritoneal cavity. Infarcted bowel always requires surgery. Most surgeons would operate on a perforated ulcer Acute pancreatitis rarely requires acute surgery. DPL can distinguish among these three conditions Aspiration cytology cannot. The presence of bile in the aspirate suggests a perforated ulcer rather than pancreatitis or strangulated bowel

The presence of a large number of bacteria in the aspirate points toward strangulated bowel rather than pancreatitis or a perforated ulcer. Furthermore, a Gram stain may reveal an occasional patient with primary peritonitis who may not require surgery The amylase level of peritoneal fluid may remain high after the serum amylase has returned to normal in patients with acute pancreatitis

It takes 2–3 h to develop a leucocyte-rich peritoneal exudate[1] If a patient with a perforated ulcer is seen early, aspiration for white cells may be negative, but DPL may reveal bile or amylase

It should also be mentioned that both aspiration cytology and DPL may be positive for white cells and/or bacteria in some causes of an acute abdomen which do not require surgery, e.g starch peritonitis, peritoneal carcinomatosis, the serositis of rheumatic fever and some cirrhotics with ascites[2]

Even though the presence of leucocytes alone in peritoneal aspirate is a highly accurate index of intra-abdominal pathology, assessment for bile, amylase and bacteria will increase the diagnostic value of the test and may help the surgeon out of a clinical dilemma.

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Hepatic resection for colorectal secondaries

Sir

I am afraid there are two unproven assumptions made by Karanjia *et al* (*Br J Surg* 1990, 77. 27–9) in their recent paper advocating a more liberal policy for liver resection of colorectal liver metastases First, although it is often quoted that 10 per cent of all patients with liver metastases might be suitable for resection, the actual proportion is likely to be much lower than this (probably less than 5 per cent) since factors other than surgical feasibility are usually taken into account (e g. age, coexisting medical conditions, etc.). In their survey, 354 liver resections were identified during a 1 year period. This represents approximately 3 per cent of all patients developing colorectal liver metastases in the UK and may well be a fairly accurate indication of the prevalence of resectable lesions

Second, although postoperative screening by means of liver ultrasound scanning would probably reveal a higher incidence of solitary metastases it is by no means certain that resection at this asymptomatic stage would enhance overall survival compared with an unscreened group diagnosed when symptomatic. As with all screening techniques the lag time bias is important and benefit can only be established by randomized prospective studies. In addition postoperative mortality and morbidity rates (which were not mentioned in the survey) would influence overall results

Nevertheless the survey is a valuable contribution and I would agree that patients with solitary (or even 2–3) colorectal metastases in the liver might be suitable for resection and careful assessment of such patients is important

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Authors' reply

Sir

In our experience patients with hepatic secondaries from colorectal cancer do not develop local symptoms until deposits are large. Resection of these lesions is often not possible or may entail complicated hepatic resection including the inferior vena cava, etc The extra operative risk incurred and the difficulty in achieving radical clearance behoves us to identify these patients at the asymptomatic stage as outlined in our article. A substantial proportion of our first 35 resected patients had deposits in excess of 15 cm We are afraid that Professor Taylor's optimism that enough is being done for these patients in the UK is misplaced.

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A Chair of Tropical Surgery

Sir

I read with keen interest Mr Holcombe's article on, 'The need for a Chair of Tropical Surgery' (*Br J Surg* 1990, 77: 3–4) The need for such a Chair cannot be over emphasized.

Much new information on tropical pathology and surgery has accumulated and needs to be carefully annotated but the resources have been a major constraint There is an amazing amount of material for research and challenging clinical situations should stimulate investigation and scholarship

Basically three categories of surgical conditions are found in the tropics. The first are what one would call universal diseases, those that can be found anywhere in the world such as duodenal ulcer. The second group are those found either exclusively or excessively in the tropics These include amoebiasis, drancontiasis, schistosomiasis, ascariasis, tuberculosis, poliomyelitis, Hansen's disease, Burkitt's lymphoma, and leishmaniasis The third group are in fact universal diseases that have developed peculiar characteristics in the tropics because of later presentation. Some assume such large dimensions, that the prefix 'giant' has been used to qualify them

The tropical surgeon is thus a surgeon that is tackling difficult cases with limited resources and even limited renumeration. The practice of surgery in the tropics calls not only for knowledge and skill but also for diligence, courage and innovation, and above all willingness to offer service for poor financial reward

Rather than establishing Institutes of Tropical Surgery in the UK or in any European country far away from the scene of action, the Royal Colleges of Surgeons should collaborate with medical schools in the Tropics and centres of excellence to develop that discipline of tropical surgery into a fully fledged specialty so that a specialty fellowship can be awarded following a prescribed training to surgeons who already hold a fellowship diploma of one of the Royal Colleges. This will fill in the gap that exists at the present time in the fellowship training overseas Surgeons-in-training from the UK and Europe could come out to this Tropical College to broaden their experience and carry out research.

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Iatrogenic pancreatitis

Sir

The excellent review by Clavien, Burgan and Moossa (*Br J Surg* 1989; **76**: 1234–43) was notable for its careful attention to detail. However, there are two points which require further clarification

In the article, aminosalicylates, cholinergic substances and chlorthalidone were all stated as 'having been clearly proved to induce pancreatitis'. This is rather misleading as only anecdotal evidence exists of these associations· more than 30 other drugs have been implicated similarly[1] Certainly, stronger evidence exists for thiazide diuretics and steroids as being causative

Secondly, although it is true that endoscopic retrograde cholangiopancreatography (ERCP) is associated with hyperamylasaemia and in some cases clinical pancreatitis, there is now good evidence that this can be reduced by the use of low osmolar, non-ionic contrast media[2,3].

The study of both these conditions is also interesting in that further light may be shed on the actual mechanism of pancreatitis

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Throwing out the baby with the bathwater

Sir

We disagree with the opinion of Turner and Murie (*Br J Surg* 1989; **76**: 1247–50), that intravenous digital subtraction angiography (IVDSA) should not be used to assess the carotid arteries in stroke patients because of unsatisfactory safety and accuracy On the question of safety, two of the most unfavourable publications were cited in which three neurological complications were reported in 602 examinations. Each happened some time after the completion of the study unlike those in intra-arterial angiography which usually happen during the procedure, characteristically immediately after an injection of contrast material, or saline. Your readers are urged to study the report of a multi-centre prospective study in which not one neurological complication occurred in several thousand IVDSA examinations and evanescent chest pain, which occurred in 0·2 per cent, was the only potentially serious systemic event recorded (Stevens *et al.*[1]) Why some workers have registered many more serious events is conjectural. The total dose of iodine given in an average IVDSA is lower than the dose recommended by some workers to enhance a routine computed tomographic brain scan. Perhaps the use of ionic rather than non-ionic contrast material was important, although far larger comparative trials have found only small differences in the low incidences of only minor complications recorded using either media (Sackett *et al.*[2], Seyferth *et al.*[3]).

On the question of accuracy, it is time it was accepted that precise grading of a carotid stenosis is not of clinical value. The few studies which consider age matched controls indicate that only severe stenosis correlates with ipsilateral cerebral hemisphere events and pathological evidence of brain damage, and then only weakly, and that all grades of stenosis less than this do not (Brown *et al.*[4], Schwartz and Mitchell[5]). Furthermore, even the best quality cut film angiography is unreliable at identifying ulcerated atheroma and adherent thrombus, and also may underestimate a stenosis (Kricheff[6]), yet so often this is taken as the standard against which other techniques are compared. Image quality in the average IVDSA is inferior to intra-arterial techniques but this does not mean the method is not clinically useful, and the 5–10 per cent of examinations which are non-diagnostic are usually easily recognizable as such by all who view them.

We agree with Turner and Murie that the frequency of complications with intra-arterial techniques is unacceptably high for screening. Carotid sonography may be satisfactory in specialized units, but usually shows only a small part of the vascular tree and can be unreliable in less committed hands Importantly the reliability of each result cannot be evaluated readily by the referring clinician

Misconceptions abound about the importance of proximal atheroma as a cause of cerebral symptoms and a realistic attitude towards our diagnostic aims is urgently required. We wish to identify not simply atheroma, which is common, but clinically relevant, atheroma which is much less common. We believe IVDSA to be a serviceable screening test for the following reasons· (1) It has an acceptably low morbidity, (2) It shows the entire vascular tree from aortic arch to Circle of Willis, and beyond, (3) It is less likely on the whole to produce an unrecognizably spurious result than carotid sonography, (4) Its sensitivity is such that it detects mainly severe atheroma which is more likely to be relevant; and (5) It can be the definitive contrast investigation in around 90 per cent of patients, including those having carotid endarterectomies (Stevens *et al* [1])

Turner and Murie have advocated that we throw out the baby with the bathwater. We are saying throw out only the muddy water and keep this particular baby at least until something better comes along.

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Author's reply

Sir

I am grateful to be allowed the opportunity to respond to the above letter, although to do so comprehensively would take more space than is available here I shall, however, address the main points I am indebted to Drs Stevens and Raphael for drawing attention to their excellent paper on the safety of IVDSA[1], although these data could not be incorporated into our survey because their publication appeared in print only in September 1989 whereas the survey in question was accepted for publication in June of that year For the following reasons I doubt whether the inclusion of their data would make much difference to our conclusions.

While I agree that the precise grading of carotid stenosis may have doubtful clinical merit, this concept is irrelevant to our study which sought simply to compare the accuracy of techniques More to the point is the claim that carotid sonography 'may be satisfactory in specialized units', and that it 'can be unreliable in less committed hands' While this may be so it is no less true, surely, for IVDSA. The study by Drs Stevens and Raphael which advocates IVDSA involves only three hospitals, two of these are London university teaching hospitals and the third is the National Hospital for Nervous Diseases. Really one must compare like with like; best quality IVDSA with best quality ultrasonography.

The five points in the penultimate paragraph of the letter may be answered as follows (1) IVDSA does not have a lower morbidity rate than ultrasonography – one of the most important aspects for your readers to consider; (2) A screening test does not need to show the vasculature from aortic arch to brain: (3) That IVDSA is less likely to produce a spurious result than sonography is very open to doubt[2,3], (4) That IVDSA detects severe atheroma better than ultrasonography is also very doubtful[4]; and (5) While it may be the case in the three specialist centres examined in their paper that IVDSA can be the definitive contrast investigation for patients having carotid endarterectomy, others seem to have a different experience[5]. In a survey of those doing this operation in the UK and Ireland in 1984 IVDSA did not seem very attractive to operating surgeons[6,7]. A more recent survey for 1989 (to be published later this year) shows that IVDSA has not become particularly popular in the intervening period. The technique may produce satisfactory images for some enthusiastic radiologists but it does not uniformly produce adequate detail for operating surgeons

In summary, IVDSA has neither the safety of ultrasonography for screening purposes, nor the confidence of surgeons generally for definitive preoperative imaging. Nevertheless, in centres of excellence with considerable experience of the technique, IVDSA may still have a role

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7. Murie JA, Morris PJ. Digital subtraction angiography and carotid artery assessment. *Lancet* 1985, **ii**· 1124.

Book reviews

Scientific Foundations of Urology. 3rd edn.

G D. Chisholm, W R. Fair 285 × 220 mm Pp. 690 Illustrated. 1990. Oxford Heinemann and Year Book Medical Publishers £80 00 hardback

Great advances have taken place since the advent of this book 14 years ago: pride of place going to new techniques of urinary stone removal which have rendered open stone surgery all but obsolete Urology is fortunate in having a book of this stature at its command as testament to the consolidation of urology as a surgical specialty.

The production of this work has been an act of faith as clinical advances are often led, not by basic science, but by developments in technology or practical surgery, the route from basic science being tenuous and the benefit delayed However, there is no doubt that the reductionist approach of basic science, exemplified by immunology and cancer biology, will have a major impact on clinical practice

Clinical and basic science aspects of most areas of urology are well covered, mainly by internationally recognized authors. It is always invidious to select particular chapters in a book of this size and quality for either praise or criticism. Certain chapters stand out: those covering the role of bacterial adherence and urinary infection, spinal injuries and cancer biology are models of clarity However, some chapters have not been well updated and refer to only few studies published within the last 10 years; it is also disappointing to see authors mainly referencing their own work Some important topics such as immunological aspects of transplantation are covered only superficially

Despite these minor criticisms, however, the book works well and a copy should grace the shelf of any urology department professing a scientific interest Urological research fellows beginning their literature review would do well to begin here and urologists seeking a wide coverage of science as applied to urology will find their needs largely met· they should buy the book.

D. Neale

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The Causation and Clinical Management of Pelvic Radiation Disease

P F Schofield, E. W Lipton. 250 × 170 mm Pp. 153 Illustrated 1989 Berlin Springer-Verlag £49 50

For most general surgeons and urologists it is a rare event to see a patient with severe radiation damage to bowel or bladder. When it does happen it is easy to overlook the radiotherapy as a cause of the symptoms since they may arise 20 or more years after treatment, and in many such instances an initial diagnosis of recurrent carcinoma is falsely made However, even for those only seeing the occasional patient an awareness of the symptoms caused by radiotherapy damage is important, as is an understanding of the now well-accepted principles of its management.

Who better to impart these principles than a multidisciplinary team from a centre that treats a large number of such patients This review comes from the Christie Hospital in Manchester which treats more cancer patients than any other centre in the UK Of course it does not necessarily follow that it will also have the biggest experience of radiation injuries, for in the past the incidence has varied between different centres and some decided to reduce both the radiation dose and the size of the fields they used because they were finding an unacceptably high incidence

This is a comprehensive review that covers the basic principles of administering pelvic radiotherapy together with the pathology, clinical findings, radiology and management of the bowel and bladder complications that may follow it – and all in a volume that can be read through in a day That must make it suitable for the Fellowship candidate or the surgeon-in-training as well as the established surgeon faced with such problems. With the 11 authors all coming from the same place one would imagine there would be strict control and coordination over the content, so it is surprising to find repetition in the book and some illogicalities of layout, such as the general pathology separated from the pathology of the vascular changes Although one wonders if a surgeon unfamiliar with radiation damage would be able, after reading this book, to recognize it when faced with its sigmoidoscopic or operative appearances, nevertheless the book does pack a lot of information into a thin volume and this makes it a welcome aid to better surgical practice

J. P. S. Cochrane

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Whittington Hospital
London
UK

Current Critical Problems in Vascular Surgery

F. J. Veith, ed 280 × 215 mm. Pp. 576 Illustrated 1988 St Louis Quality Medical Publishing. $69.95 (USA), $79 90 (International)

The book of the symposium is now common The frequent appearance of these collected monographs relates more to the economics of publishing than the need for additions to the vascular book mountain. There are currently at least four annual vascular symposia contributing to the surfeit, so overlap, repetition and old lamps masquerading as new are inevitable A halt will not be called while symposium organizers yearn to edit, guest speakers to be published and profitable sales are guaranteed through inclusive conference registration fees paid by universities, hospitals and the internal revenue service.

The merit of this book lies in the collection of diverse source material in a single readily accessible volume The reader can quickly discover whether he is still up-to-date in all areas of the specialty and correct the deficiency if he is not. Essays vary from the excellent to the embarrassingly slight; from a casual nine column inches to a conscientious 15 pages, from the generously illustrated to blank text Some articles are topical reviews specifically researched and written for the book, others comprise vintage published data from the authors prime or routine clinical audits unattractive to peer reviewed journals This book, like others of its type, is a curate's egg

J. Collin

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Oxford OX3 9DU
UK

The Cryptorchid Testis

T O Abney, B A Keel. 260 × 180 mm Pp 168 Illustrated 1989. USA CRC Press £84 00 hardback

Cryptorchidism is the single most common malformation in human males, with an incidence of 1 4 to 2 7 per cent It can be caused by anatomic malformations, genetic disorders and inborn errors of metabolism, as well as by unexplained factors Histological findings reveal damaged Leydig cells in all the above groups, but they do not show any clinical signs of androgen deficiency However, the testosterone synthesized by the Leydig cells is essential for maintaining and stimulating normal spermatogenesis, which we know to be deficient in cryptorchidism Changes in the cryptorchid testis are noted in the first 2 years of life, and there is a definite decrease in germ cell population in the contralateral gonad.

Most of the work reported in this book relates to investigations undertaken in experimentally and surgically induced cryptorchidism in animals, noting the changes in pituitary function, serum gonadotrophins, Leydig cell morphology, Sertoli cell development, etc. The effects of cryptorchidism on fertility have been stressed and, as intended by the authors, this book will I am sure enlighten the reader, as it has the reviewer However, it is not intended for the surgeon who is seeking guidance on how to manage the intra-abdominal testis or any other clinical problems

C. A. C. Charlton

Consultant Urologist
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UK

Notices and announcements

15–21 July 1990
1990 Surgical Updating in Surgery and in Surgical and Oncological Disciplines
Milan, Italy
Information: Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information: Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

25–27 July 1990
British Association of Paediatric Surgeons XXXVII Annual International Congress
University of Strathclyde, Glasgow, UK
Information. Miss D. Grant, BAPS Administrative Secretary, Royal College of Surgeons, Nicolson Street, Edinburth EH8 9DW, UK

19–23 August 1990
Recent Advances in Oral Maxillofacial Surgery
Glasgow, UK
Information: Louise Deakin, Courses dept., The British Council, 65 Davies Street, London W1Y 2AA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

28 August–7 September 1990
Recent Advances in Respiratory Medicine
Edinburgh, UK
Information: Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

1–6 September 1990
6th World Congress in Ultrasound
Copenhagen, Denmark
Information. Torben Larsen, Dept of Gynecology, Herlev Hospital, DK-2730 Herlev, Denmark

6–8 September 1990
2nd Congress of the European Association of Video-Surgery
Turin, Italy
6*Information.* Professor A. Gaetini, Torino Esposizioni Corso Massimo D'Azeglio 15-10126 Torino, Italy

12–14 September 1990
Carotid Duplex Technology, Hands-on Instruction
Northeast USA
Information Patricia Aguilar, Keith Mauney & Associates Inc, 600 E. Las Colinas Blvd, Suite 250, Irving, Texas 75039, USA

15–16 September 1990
Advanced Carotid Duplex Interpretation
Northeast USA
Information: Patricia Aguilar, Keith Mauney & Associates Inc, 600 E. Las Colinas Blvd, Suite 250, Irving, Texas 75039, USA

14–17 September 1990
Annual Meeting of RCPSC
Toronto, Canada
Information: Anna Lee Chabot, Head – Meetings and Assemblies Section, Office of Fellowship Affairs, The Royal College of Physicians and Surgeons of Canada, Toronto, Canada

20–21 September 1990
IV Annual Meeting of the European Society for Vascular Surgery
Rome, Italy
Information. Paolo Fiorani, Department of Vascular Surgery, University of Rome, School of Medicine, Policlinico Umberto 1, 00161 Rome, Italy

23–28 September 1990
Comprehensive Review and Update of What's New In Vascular Surgery
Santa Monica, California, USA
Information. Dr W S. Moore, Professor of Surgery, Section of Vascular Surgery, UCLA School of Medicine, PO Box 24901, Los Angeles, California 90024-0901, USA

25–28 September 1990
1st International Conference on Ultrasound Angiography
London, UK
Information Mr K. N. Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

26–28 September 1990
Annual Scientific Meeting
University of Manchester
Information: Ann Muir, Association of Anaesthetists, 9 Bedford Square, London WC1B 3RA, UK

1–4 October 1990
Eurochirurgie: 92e Congres Francais de Chirurgie
Paris, France
Information: Secretariat Administratif, CONVERGENCES-AFC 90, 120 avenue Gambetta, 75020 Paris, France

3–6 October 1990
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455, USA

7–12 October 1990
Future Conventions of the American College of Surgeons
San Francisco, USA
Information Fred C Spillman, Convention Manager, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

23–31 October 1990
Clinical Anaesthesia in the 1990s
Bristol, UK
Information Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

28 October–1 November 1990
43nd Postgraduate Assembly
Honolulu, Hawaii
Information. Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

2 November 1990
Management of Complications Following Vascular Surgery
Newcastle-upon-Tyne, UK
Information. Mr J Chamberlain, Ward 7 Office, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

3–7 November 1990
State of the Art in Digestive Surgery
Delhi, India
Information: Convention Centre, Hotel Taj Palace Intercontinental, Sardar Patel Marj, New Delhi 110021, India

13–16 November 1990
2nd International Interdisciplinary Symposium
Vienna, Austria
Information: Peritoneum and Peritoneal Access (PAX), F Schulz, c/o Vienna Academy of Postgraduate Medical Education and Research, Alser Strasse 4, A-1090 Vienna, Austria

6–8 December 1990
1st International Symposium on Benign Breast Disease and Chemoprevention of Breast Cancer
Genoa, Italy
Information. Oncologia Clinica, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10, 16132 Genova, Italy

11–13 December 1990
5th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Joseph W C. Leung, Senior Lecturer in Medicine, Prince of Wales Hospital, Shatin, Hong Kong

19–20 January 1991
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 January–1 February 1991
Second European Winter Oncology Conference
Meribel, France
Information: IMEDEX B,V, PO Box 3283, 5203 DG 's-Hertogenbosch. The Netherlands

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information. ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

SURGERY

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Data Sheet

PDS* and PDS II (Polydioxanone)
Sterile Monofilament Synthetic Absorbable Suture

Presentation

PDS and PDS II (Polydioxanone) Monofilament Synthetic Absorbable Sutures are prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C Blue No. 6 during polymerisation. PDS II (Polydioxanone) sutures are coloured by adding D & C Violet No. 2. PDS II sutures may also be manufactured undyed (clear). PDS and PDS II (Polydioxanone) are available attached to stainless steel needles of various types and sizes, and are sterilised by ethylene oxide gas.

PDS and PDS II (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

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Data obtained from implantation studies in rats show the following absorption profile:

14 days post implantation –
70% strength remaining
28 days post implantation –
50% strength remaining
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This indicates a significantly longer period of wound support than previously available with an absorbable suture.

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within 180 days.

Uses

PDS and PDS II (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration

By implantation.

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required or in conjunction with prosthetic devices e.g. heart valves or synthetic grafts.

The safety and effectiveness of PDS and PDS II (Polydioxanone) sutures in neural and cardiac tissue have not been established.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal epithelium sutures could cause localised irritation if left in place for longer than 10 days. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

Pharmaceutical Precautions

Recommended storage conditions are below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack. Do not re-sterilise the contents of the pack. Unused product from opened packs should be discarded.

As with all sutures, care should be taken to avoid damage when handling. Avoid the crushing or crimping application of surgical instruments such as needle holders and forceps to the strand, except when grasping the free end of the suture during an instrument tie.

Legal Category

Not applicable.

Package Quantities

PDS is available in various lengths in gauge sizes Metric 0.2 to 0.4 (10/0 to 8/0). PDS II is available in various lengths in gauges sizes Metric 0.5 to 5.0 (7/0 to 2). The sutures are packaged in sealed aluminium foil packs and peel apart overwrap pouches. The sales unit is a film wrapped box containing 12 or 24 packs.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos.

0508/0020 PDS II – Undyed
0508/0021 PDS II – Violet Dyed
0508/0022 PDS – Blue Dyed

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Contra-indications, Warnings, etc: Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis. Warnings: Use in pregnancy: There is inadequate evidence of safety in use during pregnancy. The product is of porcine origin. Rarely cases of hyper-uricosuria and hyper-uricaemia have been reported with high doses of pancreatin. Overdosage could precipitate meconium ileus equivalent. Perianal irritation could occur, and, rarely, inflammation when large doses are used. **Product Licence Number:** 5727/0001. **Name and address of Licence Holder:** Kali Chemie Pharma GmbH, Postfach 220, D-3000, Hannover 1, West Germany.

duphar Further information is available from:
Duphar Laboratories Limited, Gaters Hill, West End, Southampton SO3 3JD. Tel: 0703 472281.

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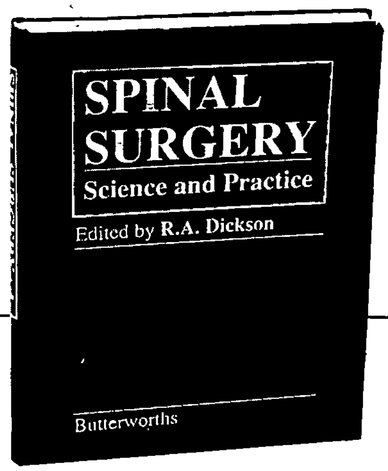

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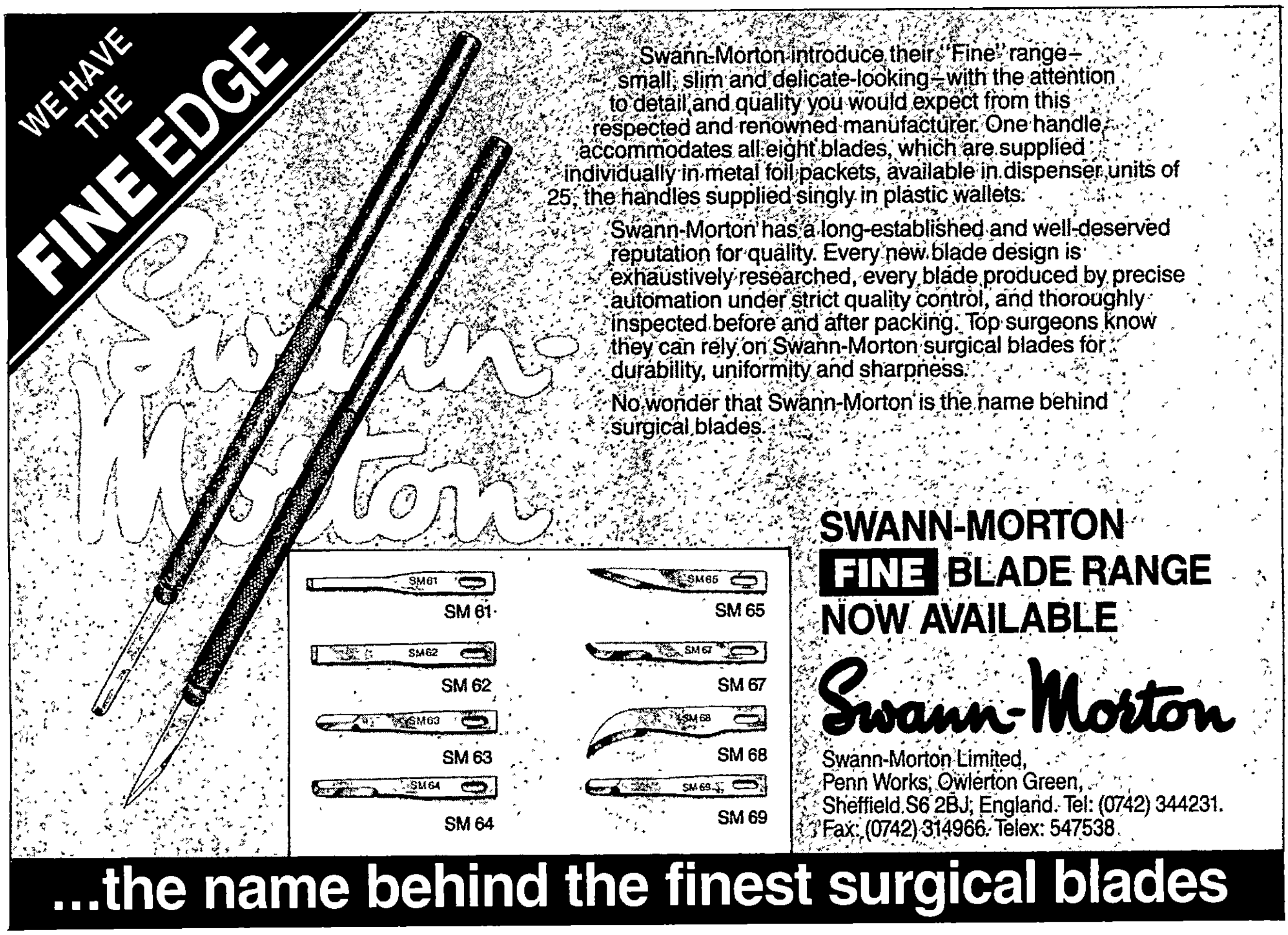

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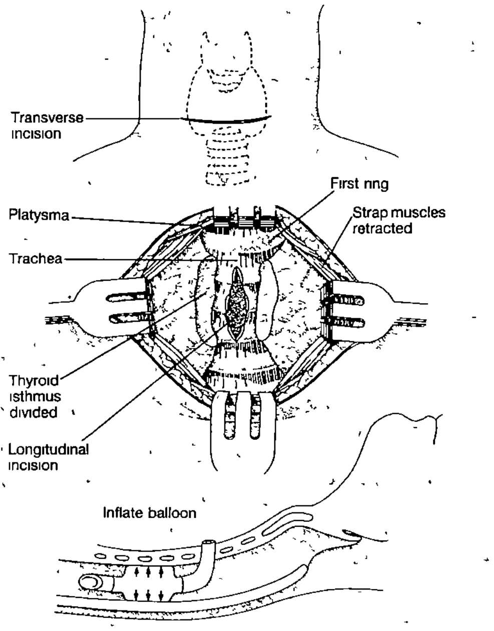

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Adjuvant therapy in colorectal cancer: the need for a mega-trial

It is now almost 30 years since randomized trials of adjuvant therapy for colorectal cancer were first reported, yet most British clinicians remain sufficiently unconvinced of the efficacy of adjuvant radiotherapy or chemotherapy to use them routinely in their practices. It cannot be said, however, that the multiplicity of trials has demonstrated a true lack of effect, but merely that they have not excluded a moderate effect on mortality rate. Most would accept that there is trial evidence that adjuvant radiotherapy causes a reduction in risk of local recurrence, but it would appear that nothing short of a convincingly demonstrated effect on mortality rate would be enough to persuade most clinicians into a change of practice. The available evidence comes from trials which involve in total less than 5000 patients, a small number considering the high prevalence of the disease (25 000 cases per year in the UK alone). A meta-analysis of the many small trials, each involving at best a few hundred patients, suggested that radiotherapy may reduce the mortality rate from rectal cancer by up to 10 per cent[1]. If the true effect were of this magnitude, it would be important – an increase in five year survival rate from 50 per cent to 60 per cent would save thousands of lives each year. The main reason for lack of confidence in the available data is that the trials were not large enough individually to detect reliably such an apparently moderate effect; they could only have demonstrated improvements in survival rates of 40 per cent or more.

A similar situation exists with regard to adjuvant systemic chemotherapy. A meta-analysis of some 20 randomized trials suggested that prolonged systemic chemotherapy regimens (containing 5-fluorouracil, 5FU) might reduce mortality rate by up to 10–15 per cent[1]. However, this difference was of marginal statistical significance, with confidence limits ranging from zero to about a 20 per cent reduction in the odds of death. To compound the level of uncertainty, adjuvant portal vein cytotoxic infusion (5FU, usually in conjunction with heparin and sometimes mitomycin-C) has been reported in several small studies (involving in all only 2000 patients) to hold promose of survival improvement. The odds ratio in meta-analysis shows a reduction in mortality rate of some 30 per cent, but again with wide confidence limits. In addition, problems with high exclusion rates and conflicting results based on stage and site of tumour add to the confusion. On the other hand, the inconvenience associated with adjuvant systemic cytotoxic therapy can be reduced by this technique since it is administered for only the first seven postoperative days, and hence completed by the time the patient leaves hospital. A further advantage relates to the very low toxicity levels reported in all trials, which makes it likely to be acceptable to both patient and surgeon.

Meta-analyses have obvious limitations[2]. However, they do suggest a way forward and there remains the very real possibility that these two treatments might have additive effects, radiotherapy reducing local recurrence and portal vein infusion diminishing the risk of overt liver metastasis. This might combine to produce an improvement in survival rate in the region of 10–20 per cent. If such a modest improvement were regarded as clinically worthwhile, it would require a large trial, involving thousands of patients, to demonstrate it convincingly. But modest improvements are far less glamorous than 'breakthroughs', and it must remain debatable whether sufficient patients could be recruited to make a 'mega-trial' successful. To achieve adequate numbers of patients, therefore, the treatments would need to be widely practicable, a large number of clinicians would need to be sufficiently interested in the question to participate, and the trial would need to be streamlined so that it would be feasible for them to do so.

An aspect of trials which detracts from recruitment of large numbers of patients is strict entry criteria, insistence on which ignores variations in individual practice, thus imposing constraints on collaborating clinicians by expecting them to deviate from what they would feel is 'comfortable' practice. Often protocols demand expensive extra investigations, and limitations in the availability of junior staff, equipment and secretarial services all detract from recruitment. So how important are strict entry criteria, rigid treatment protocols and detailed follow-up investigations?

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Recently emphasis has been placed on pragmatic trials which are designed to come much closer to daily clinical practice, and which do not demand more than minimal extra work from participants; moreover, it is argued that such trials answer questions more reliably, provided that large numbers of patients are recruited[3]. A wide range of patients will not only answer the question of whether treatment is of benefit but also which types of patient benefit most. The decision of whether a patient should be 'randomized' is based solely on whether the clinician is uncertain as to the potential benefit of adjuvant treatment; randomization becomes the instrument of treatment choice in place of some vague, empirical stab in the dark. Very fit old people are not automatically excluded, while the surgeon is not forced to randomize the unfit or nervous individual, who, his clinical sense would normally tell him, would not stand up well to the rigours of the treatment under scrutiny. This pragmatic approach has been extremely successful in trials in other specialities. A recent international cardiology trial run on these lines, for example, randomized over 17 000 patients in 5 years[4].

In 1988, the Colorectal Group of the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) sent a questionnaire to all UK surgeons, from which it was apparent that there was major interest in the questions discussed above. The AXIS Trial, designed to be large enough to confirm or refute the efficacy of adjuvant radiotherapy or intrahepatic 5 FU, alone or in combination, is the result. Trial eligibility is determined by the participants, not by the protocol. The trial has a factorial design, in which two randomizations are available – rectal cancer patients can be randomized separately to receive perioperative radiotherapy or not, and 5FU portal vein infusion or not. In colon cancer patients only the 5FU randomization is available. This design will for the first time provide data on the combined effects of these two treatments in rectal cancer, as well as reliable information on each method separately. Broad guidelines for doses and fractionation are included in the protocol, but local practice will be the main determinant of the regimen used by each clinician. No extra test or follow-up visits are required and data collection is absolutely minimal (about 10 min per patient per year). The most important datum, the death of the patient, should it occur, will be collected via the National Health Service Central Registry without bothering the clinician. Funds are available to provide clerical support for the minimal amount of extra work generated locally.

For too long there has been uncertainty; we need to know reliably whether adjuvant treatment affects mortality rate in colorectal cancer and we have a responsibility to try and find out. Most UK surgeons do not put patients into trials because of the perceived extra work load and general 'hassle' of tight protocols. The AXIS trial is designed to be as 'surgeon friendly' as possible and provides an opportunity to randomize large numbers of patients into a truly multicentre UK trial.

The AXIS Trial is funded jointly by Cancer Research Campaign, Imperial Cancer Research Fund and Medical Research Council. Any surgeon or radiotherapist wishing to receive the AXIS protocol and an explanatory video should contact: Lore Garten, MRC Cancer Trials Office, 7, Green Street, Cambridge CB2 3JU, UK. (Telephone No. (0223) 311110).

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On behalf of the Colorectal Subcommittee of the
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on Cancer Research

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Amoebic liver abscess

Management of amoebic liver abscess continues to generate considerable controversy. A number of recent studies have attempted to define more precisely the indications for needle aspiration[1,2], while the role of surgery in the management of ruptured amoebic liver abscess has also been brought into question[3,4]. Meanwhile, modern imaging techniques have improved our understanding of the patterns of resolution of successfully treated abscesses, and allowed a more objective comparison between different treatment methods, as well as permitting accurate placement of drainage catheters, thus opening up new therapeutic possibilities.

An amoebic abscess of the liver arises as a result of the spread of *Entamoeba histolytica* from the primary site of infection, the large bowel, via the portal vein. Compromised host defences may be important in allowing the establishment of hepatic infection with subsequent abscess formation. The abscess is usually solitary and in the right lobe, and men are more commonly affected than women. Diagnosis requires a high index of suspicion. Right upper quadrant pain, fever and tender hepatomegaly are the predominant clinical features. In more advanced cases a tender mass may be both palpable and visible. Leukocytosis and raised alkaline phosphatase are common, but jaundice is unusual. Clinical and radiological changes at the lung base (especially on the right) often provide a useful clue to the diagnosis. Ultrasonography and other imaging techniques are useful in confirming the presence of a mass or masses, but cannot distinguish between pyogenic and amoebic abscess[5]. Indeed it may not be possible to distinguish reliably between abscess and carcinoma with these techniques[6]. Confirmation of the diagnosis therefore depends on serological tests and response to treatment. A minority of authors employ initial routine diagnostic fine needle aspiration to exclude pyogenic abscess.

Most amoebic abscesses of the liver respond to medical management, and metronidazole is the amoebicide of choice. A number of studies have been undertaken in an attempt to define more clearly the indications for needle aspiration of amoebic liver abscess. De la Rey Nel *et al.*[2], combining the results of a retrospective and prospective study, suggested that aspiration was indicated in the following circumstances: no clinical improvement within 48–72 h, abscesses causing marked tenderness or severe pain, abscesses greater than 10 cm in diameter, marked elevation of the diaphragm, most left lobe abscesses, and abscesses associated with negative serological tests. Their study also indicated that a distance of 2·5 cm from the diaphragm was 'safe'. These indications were based on the finding of a shorter duration of tenderness in the aspirated group (prospective study), and a higher complication rate in the non-aspirated group (retrospective study). Incorrect diagnosis was a major cause of morbidity and mortality, hence the importance of confirming the diagnosis serologically in those managed without aspiration. Sharma *et al.*[1] reported the results of a randomized case-control study comparing patents treated with metronidazole alone in a daily dose of 2·4 g for 10 days with a group of patients who had needle aspiration in addition to metronidazole. The mean diameter of liver abscess measured by ultrasound was 72 mm and 54 mm, respectively. Patients with left lobe abscesses, multiple abscesses, and those where abscess rupture appeared imminent were excluded from the study. All patients were asymptomatic within 3 weeks, and remained so 1 year later. The authors concluded that routine aspiration of uncomplicated amoebic liver abscess is unnecesary. Given the exclusion criteria and the abscess sizes, the findings of this study are not at variance with those of de la Rey Nel *et al.*[2].

Resistance to drug treatment is also a well recognized problem. Singh and Kashyap[7] prospectively studied resistant amoebic liver abscesses and compared four different treatment methods: repeat trial of conservative therapy, therapeutic needle aspiration, percutaneous catheter drainage, and open surgical drainage. No failure of therapy was seen with percutaneous catheter drainage or open surgical drainage, but percutaneous catheter drainage was associated with more rapid symptom relief and a shorter hospital stay.

Modern imaging techniques (such as ultrasound, scintigraphy, computed tomography scan and magnetic resonance) have not only an important role in diagnosis and in guiding drainage catheter placement, but also have added considerably to our knowledge of the patterns of resolution which follow successful treatment. Ahmed *et al.*[8] studied 25 patients with amoebic liver abscess and found that larger abscesses took longer to resolve than smaller ones but that complete resolution occurred in all patients, the longest taking 20 months to do so. Most of

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the abscesses larger than 10 cm in diameter required more than 1 year to resolve. The authors found that aspiration did not speed resolution, but there were only three patients treated in this way. In the study by Sharma *et al.*[1], although all patients were asymptomatic at 1 year, only 11 of 37 patients had complete resolution of the abscess cavity, and the overall mean diameter of the residual abscess cavity was 21–25 mm. In another prospective study, Sheen *et al.*[9] compared the resolution of pyogenic and amoebic liver abscesses. They found that pyogenic abscesses resolved more rapidly than amoebic abscesses, and that in three of the amoebic group, the cavity was still detectable on ultrasound examination after 2 years. They stressed the importance of this finding in regard to the differential diagnosis of space-occupying lesions in the liver, particularly as many parts of the world have a high incidence of both amoebic abscess and hepatocellular carcinoma.

An amoebic liver abscess may rupture into the pleura and lung, peritoneal cavity, or pericardium. The management of intraperitoneal rupture is controversial, with most surgeons recommending operative management[10]. However, this policy has recently been questioned. Sarda *et al.*[3] retrospectively analysed 23 cases of amoebic liver abscess complicated by intraperitoneal rupture, and concluded that if an early diagnosis could be made, conservative treatment (metronidazole, broad-spectrum antibiotics, chloroquine, and needle aspiration of liver abscess) offered the best chance of cure. Ken *et al.*[4] reported five patients with perforated amoebic liver abscess all successfully managed by percutaneous catheter drainage and metronidazole. Multiple catheters were required in four of the five patients, and all associated fistulae healed without surgery. A reluctance to institute conservative management in patients with features of generalized peritonitis might be overcome if laparoscopy were employed to ensure adequate peritoneal toilet and accurate catheter placement, in addition to providing certain confirmation of the diagnosis. This potential use of the laparoscope has, to my knowledge, yet to be tried in practice.

In conclusion, uncomplicated amoebic liver abscess usually responds to medical therapy, and the indications for needle aspiration have been recently more clearly defined. Complicated cases are best managed by adjuvant guided percutaneous catheter drainage, and open surgery is now seldom indicated. Despite successful therapy, complete resolution of the abscess cavity may take several years.

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Surgical therapy of oesophageal carcinoma

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During the past 10 years, postoperative mortality associated with surgical treatment of oesophageal carcinoma has been reduced by one-half. However, it appears that all efforts to improve long-term survival with extensive excisional procedures and adjuvant chemotherapy and radiotherapy have failed. Fifty-six of 100 patients presenting to the surgeon with an oesophageal carcinoma have resectable disease. Recent studies suggest that seven of them will die from postoperative complications and 49 patients will be discharged from the hospital after an average of 3 weeks. Of these patients, 27 will survive the first, 12 the second, and ten the fifth year. Although it may be possible to further reduce postoperative complications and mortality, the chances of improving the long-term prognosis of patients with oesophageal carcinoma seem small.

Keywords: Oesophageal carcinoma, surgery, adjuvant therapy

Earlam and Cunha-Melo[1] published a critical review of the results of the surgical treatment of oesophageal carcinoma in 1980 Their analysis of the literature on oesophageal carcinoma during the 25 year period from 1953 to 1978 (*Table 1*) set the standard for therapy. However, hospital mortality has been reduced substantially during the past 10 years by the introduction of prophylactic antibiotics, perioperative parenteral nutrition or tube feeding, and by improvements in anaesthesia, surgical techniques and intensive care medicine. Extended resection procedures such as posterior mediastinectomy[2], the '*en-bloc*' resection[3] and the use of adjuvant chemotherapy and/or radiotherapy raise hope that long-term prognosis may improve as well. The purpose of this study is to review the results of surgical therapy during recent years.

Materials and methods

The treatment outcome from 1201 papers on surgical treatment for oesophageal carcinoma have been reviewed All papers published during the period 1 January 1980–31 December 1988 were reviewed, if they contained at least a summary written in a West-European language. A large number of the articles found by computer-aided literature search (German Institute of Medicine Documentation and Information), however, proved to be unsuitable for subsequent analysis either because they did not contain sufficient details for statistical evaluation (editorials, letters, etc) or because surgical therapy did not represent the main focus of the paper (*Table 2*) Studies including less than 50 patients were included only if they dealt with adjuvant therapy If an author had published his updated results several times during the search period, only the most recent article was evaluated, unless a previous paper contained more detailed information on a certain operative technique. Papers were also excluded if the majority of the patients suffered from adenocarcinoma rather than squamous cell carcinoma

More than 90 per cent of the malignant tumours found in the oesophagus are squamous cell carcinomas 'True' adenocarcinomas originating from ectopic gastric mucosal islets in the oesophagus account for 5–7 per cent of all oesophageal malignancies[4] Nevertheless, the proportion of adenocarcinomas exceeded 15 per cent in more than half of the papers cited in *Table 3* Adenocarcinomas of the oesophagogastric junction were classified as oesophageal carcinomas if most of the tumour mass was located in the oesophagus Thus such patients had been operated on according to the principles applying to distal squamous cell carcinoma. Arguments in favour of combining these two pathologically different types of carcinoma are that in symptomatology, hospital mortality and long-term prognosis, tumours fulfilling the above mentioned criteria resemble oesophageal rather than gastric carcinomas. All papers selected for analysis (*Table 3*) were evaluated by a surgeon experienced in oesophageal carcinoma surgery using a documentary and scoring system especially developed for this review. Short-term and long-term results of special surgical techniques or adjuvant treatment methods were only tabulated if sufficient information was given. General terms, e g 'preoperative chemotherapy', without data on the drugs used and their dosages, or 'lymphadenectomy', without specification of the lymph node regions removed, were not used for detailed evaluation Long-term results given only as survival curves were digitized and calculated using a graphics computer program. Data were accumulated and evaluated on an IBM AT 3 Personal Computer

Table 1 *Results of surgical treatment of oesophageal carcinoma from 1953–1978 as compiled by Earlam and Cunha-Melo[1] in 1980 Values are given as mean(s.d.)*

No of papers	122
No of patients	83 783
Operations (%)	58(24)
Resections (%)	39(22)
Resection mortality rate (%)	29(16)
1-year survival rate (%)	18(13)
2-year survival rate (%)	9(7)
5-year survival rate (%)	4(3)

Table 2 *Reasons for exclusion of a paper*

Reason	No. of papers
Publications not available	14
Editorials or literature reviews	183
Case reports	84
Primarily laser therapy	71
Primarily radiotherapy	60
Primarily chemotherapy	31
Pathology reports	25
Anaesthetic problems	54
Abstracts	48
Letters	23
Animal experiments	2
Mixing of malignant and benign disease	41
Primarily adenocarcinoma of the cardia	70
Primarily head and neck carcinomas	53
Re-publications of the same material	191
No of patients <50	74

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Table 3 *Data from 130 papers (76 911 patients) on oesophageal cancer surgery*

							Survival rate (%)				
First author (reference)	Year	Country	No of patients	No of resections	Resection rate (%)	Hospital mortality rate after resection (%)	Year 1	2	3	4	5
Abo[5]	1986	Japan	315	260	83	9	48				16
Akiyama[6]	1980	Japan	429	279	65	1	83		32		27
Ancona[7]	1982	Italy	1279	345	27	9					
Barbier[8]	1988	Switzerland		50			57	34	23		
Barbier[9]	1988	Switzerland		50		2					
Baulieux[10]	1985	France		223		12 (10)†	49	25	14	11	9
Becker[11]	1984	Germany		67		15					
Berkoff[12]	1980	Germany	458	117	26	21		46			26
Bertelsen[13]	1985	Denmark	364	189	52	24	42	25	18	15	15
Bluett[14]	1987	USA	311	104	33	10	53	27	13	11	11
Blum[15]	1987	Germany		210		8					
Bosch[16]	1980	USA	331	81	24	25	42	21	17	14	12
Cooper[17]	1981	Canada		104		8	40	26	20	11	
Couraud[18]	1982	France		256		7	57	38	27	22	20
Dark[19]	1981	Great Britain	772	449	58	8	59	46	27	21	18
Delaby[20]	1980	France		54		9					
Delacroix[21]	1985	France		100		6					
Desai[22]	1986	India	434	404	93	6			20		6
Ellis[23]	1985	USA	219	191	87	2	68	42	31	24	16
Endo[24]	1987	Japan		906			55	34	28	23	23
Endo[25]	1984	Japan		1 190		5 (1)†					
Faller[26]	1987	Hungary	222	117	53	17					
Favre[27]	1984	France		152		18					
Fekete[28]	1987	France	320	185	58	6	79	52	46	32	24
Froelicher[29]	1986	Switzerland		51		14					
Fuentes[30]	1984	France		200		15 (10)†					
Fujimaki[31]	1987	Japan		72		7	69	42	36	33	29
Galandiuk[32]	1985	USA	238	84	35	7	52	32	19	17	14
Gatzinsky[33]	1985	USA	185	102	55	18	52	29	18	13	11
Gignoux[34]	1984	France		186		10 (6)†	71	34	27	18	13
Gignoux*[35]	1987	France	208	162	78	22	65	47	38	26	21
Gignoux*[36]	1984	France		730		13 (5)†					
Giuli*[37]	1980	France		2400		30	44	27	19	16	14
Giuli*[38]	1986	France		750		15					
Griffith[39]	1980	USA	513	211	41	11			26		14
Guerkan[40]	1987	Turkey		67		6		21			13
Hambraeus[41]	1988	Sweden		66			60	35	26	19	17
Hambraeus[42]	1981	Sweden		50		26	42	26	22	20	19
Hankins[43]	1982	USA	161	83	52	11	40	19	8	7	
Hennessy[44]	1986	Ireland	230	200	87	18	40	28	20		20
Hopkins[45]	1984	USA		54		15					
Horvath[46]	1987	Hungary	542	298	55	15	72		23		15
Huang[47]	1985	China	1 874	1 572	84	4	70		39		30
Husemann[48]	1985	Germany		110		32					
Iizuka[49]	1985	Japan	1 436	535	37	8					21
Iizuka[50]	1983	Japan	364	287	79	4	61	34	30	26	23
Iizuka*[51]	1987	Japan	7 742	4 376	57						61
Iizuka*[52]	1980	Japan	267	199	75	7	65				
Ishida[53]	1987	Japan		145		0	63	40	32	29	29
Isolauri[54]	1987	Finland	451	248	55	16	42	20	13	12	11
Isono[55]	1987	Japan		815		5 (2)†					20
Jobsen[56]	1986	Netherlands	182	69	38	19	65	48	42	40	
Kakegawa[57]	1986	Japan	206	147	71	6					21
Kasai[58]	1987	Japan	1 036	779	75	13 (3)†	68	47	37	33	29
Kasai*[59]	1986	Japan	10 113	6 130	61	8	58	37	30	26	24

Table 3 (*Continued*)

First author (reference)	Year	Country	No. of patients	No. of resections	Resection rate (%)	Hospital mortality rate after resection (%)	Survival rate (%) Year 1	2	3	4	5
Keagy[60]	1984	USA		60		7	46	27	10		5
Kessler[61]	1984	Germany		125		26 (18)†					
Kinoshita[62]	1982	Japan		1 329		6 (4)†	60	34	27	22	19
Kodama[63]	1987	Japan	144	122	85	4	52	43	32	30	25
Kuhrmeier[64]	1987	Switzerland		63		6	56	29	16	16	
Kunath[65]	1983	Germany		61		28					
Lam[66]	1982	China	304	174	57	33	52	41			
Launois[67]	1983	France	360	254	71	18 (3)†	59	33	22	13	6
Leichman[68]	1984	USA	189	113	60	15					
Li[69]	1981	China	1 079	664	62	6					25
Liu[70]	1986	China	245	184	75	7	67	48	32	30	30
Lu[71]	1987	China	1 654	1 025	62	5					24
McFarlane[72]	1988	USA	136	83	61	7	57	36	19	18	11
Mailett[73]	1982	France		271		17 (5)†	61	32	17	10	9
Mannell[74]	1987	South Africa		92		12	55	31	18		10
Mathisen[75]	1988	USA		104		3	72	38	20	17	15
Matthews*[76]	1986	Great Britain	4 680	1 119	24	32					13
McKeown[77]	1985	Great Britain	478	452	95	10	65	45			
Mitomi[78]	1987	Japan		329			95	91	86	78	74
Morand[79]	1984	France		175		18	63	35	26	22	15
Moreno[80]	1982	Spain	106	85	80	21					
Moreno[81]	1986	Spain		91		10					
Mori[82]	1986	Japan		92		0	61	50	38	38	38
Morita[83]	1985	Japan	249	130	52		56	35	26	23	23
Mueller[84]	1988	Germany	697	279	40	25 (11)†	60	38	29	26	23
Murakami[85]	1987	Japan	263	227	86						35
Nishi[86]	1988	Japan		50		8 (0)†					
OESO[87]	1984	France		763		15	45	27			
Ong[88]	1980	China		119		40	52	25	15	14	14
Orel[89]	1981	Yugoslavia		196		22					22
Orringer[90]	1987	USA		147		6	55	34	24	21	21
Parisot[91]	1985	France	225	62	28	37	35	19	16	12	7
Parker[92]	1985	USA	1 038	255	25	29 (13)†		28			
Pastorino[93]	1987	Italy		340		19	48	27	19	14	12
Pate[94]	1983	USA	642	83	13	18	41	18	10	8	8
Peracchia[95]	1982	Italy	838	260	31	11					
Peracchia[96]	1987	Italy		127		13 (0)†					
Pistolesi[97]	1984	Italy	117	57	49		25				
Plukker[98]	1988	Netherlands	96	57	59	23 (5)†	64	38	20	20	20
Poplin[99]	1987	USA	128	55	43	15					
Postlethwait[4]	1986	USA	963	301	31	18	36	17	9	7	6
Pralat[100]	1983	Germany		162		15	62	32	11	9	6
Ribet[101]	1986	France	1 367	478	35	23 (18)†	65	30	19		10
Richelme*[102]	1986	France	3 104	2 104	68	17		36			19
Roeher[103]	1988	Germany		75		11	49	20	20		
Roka[104]	1981	Austria		74		36					
Saeger[105]	1987	Germany	141	83	59	18 (7)†					23
Sasaki[106]	1987	Japan		349		6					21
Schattenkerk[107]	1987	Netherlands	525	224	43	14 (5)†	62	47	32		
Shahian[108]	1986	USA		95		8	50	35	22	19	
Shao[109]	1985	China	3 155	2 890	92	4	86	72	52	41	37
Shiozaki[110]	1987	Japan		209		7					24
Siewert[111]	1988	Germany	355	257	72	12					19
Skinner[112]	1986	USA		132		10	53	30	22	21	16
Skinner*[113]	1987	USA	3 262	1 323	41	9		35	21		13

Table 3 (*Continued*)

First author (reference)	Year	Country	No. of patients	No. of resections	Resection rate (%)	Hospital mortality rate after resection (%)	Survival rate (%) Year 1	2	3	4	5
Soga[114]	1983	Japan		206		6	57	38	33	28	26
Sombrowski[115]	1983	Germany	667	254	38	33	51		53		35
Sorrentino[116]	1987	Italy	794	240	30		70	42	34	21	21
Sugimachi[117]	1987	Japan	409	259	63	6	56	28	22	18	17
Tam[118]	1987	China		100		5					
Tanaka[119]	1987	Japan		124			51	33	24	22	21
Tremolada[120]	1984	Italy		463		10					
Tryzelaar[121]	1982	USA	81	73	90	3					
Ulrich[122]	1984	Germany	524	201	38	29 (16)†	34	24			
Veiga[123]	1984	Portugal	156	59	38	15					
Wang[124]	1983	Taiwan	1 450	642	44	6	40	20	15	12	12
Watanabe[125]	1987	Japan		158			56	33	25	22	21
Welvaart[126]	1980	Netherlands	133	63	47	25		27			
Wilkins[127]	1980	USA		72			32	14	10	8	7
Wong[128]	1987	China	378	232	61	7	43	28	24	24	
Wu*[129]	1982	China	13 707	10 464	76	4					26
Wu[130]	1984	China		751		7 (2)†	70	45	34	28	23
Xu[131]	1983	China	850	664	78	10					22
Yamada[132]	1985	Japan		1 196			60	36	28	25	23
Zilberstein[133]	1987	Brazil		73		14					

Mean(s.d.):	No. of patients resected (%)	56(21)	3-year survival rate (1)	25(12)
	Resection mortality rate (%)	13(8)	4-year survival rate (%)	21(11)
	1-year survival rate (%)	56(13)	5-year survival rate (%)	20(11)
	2-year survival rate (%)	34(12)		

* Collective review; † hospital mortality rate of last series

using dBase III Plus (Ashton Tate, Maidenhead, UK) and BMDP (BMDP Statistical Software, Los Angeles, California, USA) software Groups were compared by paired and unpaired Student's t tests when indicated ($P < 0.05$ was considered significant). All results (mean(s d.), median, total range) are expressed as rounded whole numbers.

Operability and resectability

The terms 'operable' and 'inoperable' imply that a certain number of patients may be able to undergo particular surgical procedures whereas others may be unfit because of debilitation or otherwise impaired condition The terms 'resectable' and 'unresectable' address the question of whether the removal of a growth is technically feasible and reasonable. Exact definitions of these four terms are mandatory for a generally acceptable statement on operability and resectability of patients with oesophageal carcinoma and for the comparison of treatment results in different countries or institutions. Unfortunately none of the papers provided these definitions.

We do not report an operability rate because only a minority of the authors summed all their different operations. No general rules on contraindications to surgery for oesophageal carcinoma can be given, since the risk for the patient depends on the magnitude of operative trauma. Operative trauma varies considerably from procedures such as implantation of an endo-oesophageal tube to 'blunt' dissection to transthoracic resection. Even for a single type of operation, e.g. transthoracic resection, there was no agreement among authors on which tests were necessary to assess general operability. Preoperative evaluation ranged from clinical impressions after moderate physical exercise (e.g. climbing stairs) to non-invasive tests of pulmonary, cardiac and metabolic function and invasive procedures, such as coronary angiography. Although some of these methods helped to identify high-risk groups and to define limits up to which resection could be performed without undue operative risk, their predictive value for an individual patient frequently approximated the value of flipping coins[84,134].

The resectability rate (69 authors) was 56(21) per cent. Only one study[125] evaluated all patients with oesophageal carcinoma treated by different therapeutic methods during 1981 in a region with a population of 3·7 million people. Forty-nine of 440 patients with oesophageal carcinoma underwent resection. These numbers indicate that most resectability rates provided by the authors do not allow a general statement on resectability of oesophageal carcinoma but rather that statistics reflect the situation at a particular hospital. This again is influenced by the preselection of referrals and the aggressive or conservative attitude of the operating surgeon. If a surgeon regarded even a partial or so called 'cleaning' resection of an unremovable oesophageal carcinoma as a worthwhile procedure[10,23], the percentage of resections increased to over 80 per cent and resectability and operability became almost identical terms. For a majority of surgeons, however, resection was contraindicated if widespread infiltration of adjacent organs (such as the lung, trachea, heart or major vessels), diffuse pleural or peritoneal carcinomatosis, major involvement of abdominal lymph nodes or distant organ metastases were present.

Standard resection therapy (*Table 4*)

Standard resection

The oesophagus was resected and replaced in one session by 98 per cent of all authors. Operations with an interval of 48 h[111] to several weeks[5,43,102] between resection and replacement theoretically halved the operative trauma but clinically did not reduce either hospital mortality rate or the number of postoperative complications.

The type of resection depended mainly upon the location of the primary tumour. No correlation could be found between

Table 4 *Standard resections for oesophageal carcinoma as performed by a certain number of authors*

	Location of the oesophageal carcinoma					
	Cervical	Thoracic				
		Not defined	Upper third	Middle third	Lower third	Gastric junction
Resection						
Cervical oesophagus						
Plus hypopharynx, larynx	3					
Plus hypopharynx, larynx, blunt dissection of thoracic oesophagus	14					
Thoracic oesophagus						
Right thoracic approach						
Intrathoracic anastomosis	25	5	13	1	5	
Cervical anastomosis		16	14	16	4	1
Left thoracic approach		1				7
Thoracoabdominal approach	2		2	4	17	
Blunt dissection		16	5	5	4	8
Lymph node dissection						
Thoracic	9	21	11	13	6	19
Abdominal	5	14	7	9	5	10
Reconstruction						
Stomach	14	56	20	31	13	31
Pyloroplasty	11	31	11	16	6	14
Kocher's manoeuvre	9	11	5	7	2	5
Colon		3	2		1	
Jejunum	3					5

the extent or grade of the carcinoma and the type of excision (simple resection, resection with systematic dissection of thoracic, abdominal, and eventually cervical lymph nodes, or *en-bloc* resection) Because results from prospective, randomized trials are not available and, retrospectively, none of the currently used procedures demonstrated clear advantages, the decision for limited or extended resection was based primarily on the surgeon's experience and his attitude (aggressive *versus* conservative) in the management of oesophageal carcinoma. However, there was a tendency to abstain from systematic lymph node dissection if the carcinoma extended to structures outside the oesophagus[6,112]

In cervical oesophageal carcinoma, oesophagopharyngolaryngectomy in combination with blunt dissection of the thoracic oesophagus was preferred.

For carcinomas at the thoracic inlet, the pharynx was not routinely removed. Resection was performed using either a cervical and transthoracic approach or a median sternotomy with an additional blunt dissection of the thoracic oesophagus[6,58,66,128].

For treatment of intrathoracic oesophageal carcinoma, the thoracic and abdominal portions of the oesophagus have to be excised. Most authors performed a three-phase operation as advocated by McKeown[77] or Ong *et al.*[88], if the tumour was located in the upper third of the thorax, with transection of the oesophagus in the neck using, for anatomical reasons, a left sided incision along the median border of the sternocleidomastoid muscle. If a proximal resection margin of more than 10 cm could be obtained[118], it was apparently of minor importance whether the oesophagus was transected high in the chest or via an additional cervical incision Less than 2 cm of length is gained if a cervical approach is used[128] Transthoracic operations without exposure of the oesophagus in the neck (in blunt dissection the latter is obligatory) had the advantage of a somewhat shorter operating time and a smaller chance of lacerating the recurrent laryngeal nerve. Disadvantages included a more demanding operative technique (especially if the anastomosis had to be carried out at the apex of the thorax without the aid of a stapling device) and a life threatening situation if anastomotic insufficiency developed. Although with intrathoracic anastomoses, leakage was significantly less frequent than with cervical (59 authors: 11(6) *versus* 19(15) per cent), the mortality rate was three times higher (69(16) *versus* 20(11) per cent).

Most authors felt that adenocarcinomas of the gastro-oesophageal junction required only partial resection of the thoracic oesophagus. Excision up to the lower edge of the azygos vein or the aortic arch respectively usually seemed sufficient.

A right posterolateral thoracotomy was preferred for resection of intrathoracic tumours. This approach permitted easy access to all parts of the thoracic oesophagus. Only the azygos vein, which can be ligated without sequelae, has to be transected to completely remove the oesophagus. Chinese surgeons[47,129,130] preferred a left thoracic approach, claiming that the crossing of the oesophagus by the aortic arch did not make the operation more difficult. Outside China, the left-thoracic approach is commonly used only for carcinomas of the gastro-oesophageal junction.

Blunt dissection

During recent years, an increasing number of authors have favoured transhiatal resection without thoracotomy (the so called blunt or 'blind' dissection) of the oesophagus as an alternative to transthoracic resection because this procedure theoretically reduces the operative risk to the patient. An adequately designed comparative trial is not available to validate this hypothesis. Institutions in which resections with and without thoracotomy are performed have reported, with one exception[136], comparable or lower hospital mortality rates and postoperative complication rates for blunt dissection.

It has been shown[137] that a combination of a thoracotomy wound with an upper abdominal incision produces greater disturbance in respiratory function than either incision alone. Therefore, blunt dissection has been preferred by some surgeons in patients with impaired respiratory function who appear unsuitable for transthoracic resection[28]. One might speculate that a selection bias is responsible for the similar postoperative results of resection with and without thoracotomy and that the theoretical advantage of blunt dissection has a real clinical basis.

Contraindications to transhiatal oesophagectomy included pre- or intraoperative evidence of tumour invasion of surrounding structures proximal to the tracheal bifurcation[138]. Distal to this level, however, even infiltrative carcinomas have been dissected under direct vision through the hiatus. A surgeon performing a transhiatal oesophagectomy must be willing and able to open the thorax and to resect the oesophagus in case of unexpected tumour fixation or emergency such as uncontrollable haemorrhage or laceration of the trachea.

Lymphadenectomy

Systematic dissection of intrathoracic lymph nodes as described by Akiyama[139] was a part of routine oesophageal resection for half of the authors However, some authors implied that this was restricted primarily to patients in good or excellent general health, because it may cause severe postoperative pulmonary complications[53,82,139]. Approximately one-third of the surgeons removed the paracardial, left gastric, lesser curvature, coeliac axis, splenic and common hepatic artery lymph nodes. Only a few authors[57,85,106,111,140,141] excised cervical nodes. The relatively low rate of systematic lymph node dissection, if one compares the figures with those for other malignancies, can in part be explained by our selection criteria (see Materials and methods) We reviewed papers only if the authors described their procedures in detail. However, quite a number of authors felt that oesophageal carcinoma was a systemic rather than a regional disease if the tumour had penetrated the muscular wall or infiltrated regional lymph nodes Their goal was palliation, achieved with the lowest possible operative risk.

Replacement

If not affected by disease or previous operation the stomach was the preferred organ for replacement of the oesophagus, followed by the colon. Either the left or right side of the large bowel was utilized with equal facility. Small intestine was used mainly after distal partial oesophagectomy with proximal or total gastrectomy. Free intestinal transplants have been increasingly used to replace the cervical oesophagus. As shown in two prospective, randomized trials[142,143], pyloroplasty is not required to improve gastric emptying following oesophagogastric anastomosis, even though the patient undergoes bilateral vagotomy.

Postoperative results of resectional therapy

Postoperative complications

Postoperative complications occurred in 36(28) per cent of 46 692 patients. It can be assumed, however, that a considerably higher percentage of patients experienced a complicated postoperative course, as a majority of authors report only the most serious complications or those directly related to a certain operative technique. Anastomotic insufficiency and pulmonary complications following resection with or without thoracotomy were analysed in detail, because their genesis and occurrence rate have been felt to be related to particular operative techniques.

The incidence of anastomotic leakage is influenced by a variety of conditions including cancer hypercatabolism, malnutrition, anastomotic vascular deficit, anastomotic tension and surgical technique[6,7,87]. Only a few of the studies were suitable for statistical evaluation.

Leakage rates following gastric replacement of the oesophagus and intrathoracic anastomosis were similar, whether a one layer ($n=3648$; leakage rate 12(7) per cent, median 9 per cent, range 25) or a two layer ($n=5078$; leakage rate 12(8) per cent, median 10 per cent, range 36) anastomosis was used and whether the anastomosis was carried out by hand ($n=8726$; leakage rate 11(8) per cent, median 9 per cent, range 36) or by means of an EEA-stapler (US Surgical Corporation, Norwalk, Connecticut, USA) ($n=1964$; leakage rate 13(9) per cent, median 9 per cent, range 26) When non-absorbable suture material was used, leakage rates were significantly higher ($n=1222$; leakage rate 11(8) per cent, median 9 per cent, range 23) than with absorbable material ($n=1737$; leakage rate 7(5) per cent, median 6 per cent, range 16). Comparison of pulmonary complications following transhiatal ($n=1886$) or right transthoracic ($n=2436$) resection with cervical anastomosis was difficult because no author defined complications precisely. If one compares the three entities mentioned most frequently, namely pneumonia, respiratory insufficiency and atelectasis, it appears that impaired pulmonary function was seen more often following transthoracic than transhiatal resections (21(3) *versus* 26(22) per cent; 27(19) *versus* 13(8) per cent; 23(31) *versus* 10(7) per cent, respectively).

Hospital mortality

The average hospital mortality rate following resection of oesophageal carcinoma was 13(8) per cent (median 11 per cent, range 40). It has been more than halved during the last decade, when compared with the figures (*Table 1*) reported by Earlam and Cunha-Melo[1] in 1980. That this decrease in hospital mortality rates and a trend to even lower mortality rates in the near future exists in reality is supported by the following comparisons. Papers in which observations started before 1960 reported a hospital mortality rate of 18(17) per cent (median 10 per cent, range 51) whereas the mortality rate was 11(11) per cent (median 8 per cent, range 52) if only resections performed since 1980 are evaluated. Twenty-one authors differentiated their results for oesophageal resection related to changes in operative technique or perioperative management over a certain time span. Hospital mortality rates dropped from 21(17) per cent (median 22 per cent, range 45) in their first series to 7(5) per cent (median 5 per cent, range 18) in the last.

There is no evidence that tumour-related factors determined mortality rate following oesophageal resection. Surgeons reporting only on squamous cell carcinoma found a similar hospital mortality rate (13(12) per cent, median 10 per cent, range 52) as those mixing squamous cell and adenocarcinoma (14(10) per cent, median 14 per cent, range 50). In 12481 resections, hospital mortality rate was related to the location of the growth. No significant differences were found between cases of carcinomas in the upper (18(11) per cent, median 17 per cent, range 32), middle (20(11) per cent, median 22 per cent, range 41) or lower (17(11) per cent, median 17 per cent, range 29) portions of the thoracic oesophagus nor the oesophagogastric junction (17(11) per cent, median 15 per cent, range 41). In 1322 resections data were available concerning outcome according to different tumour stages Mortality rates were 14(12) per cent (median 11 per cent, range 31) in stage I, 16(12) per cent (median 12 per cent, range 28) in stage II, 11(8) per cent (median 8 per cent, range 25) in stage III and 18(2) per cent (median 18 per cent, range 5) in stage IV cases. Hospital mortality rate was significantly lower in 13061 resections performed with curative intention (11(7) per cent, median 11 per cent, range 27) than in 16024 palliative resections (19(8) per cent, median 18 per cent, range 29).

Although discussion still continues concerning which resection technique carries the lowest risk for the patient, only minor differences in hospital mortality rates were found. Removal of the oesophagus by a left or a right transthoracic approach with intrathoracic anastomosis was associated with almost identical mortality rates (17(16) per cent, median 14 per cent, range 42 *versus* 16(11) per cent, median 13 per cent, range 47 respectively). Transthoracic resection with cervical anastomosis reduced this figure to 12(10) per cent (median 10 per cent, range 40). The lowest mortality rate was found with blunt dissection of the oesophagus (11(8) per cent, median 8 per cent, range 30). When comparing these data, one must remember that transhiatal resection, introduced in most surgical departments only recently, has the benefit of recent advances in perioperative care. However, blunt dissection was restricted to high-risk patients in some institutions.

Remarkable differences in hospital mortality rates were found when the reports were analysed according to their country of origin. In Japan, mortality rates were considerably lower (6(3) per cent, median 6 per cent, range 10) than in Italy (12(4) per cent, median 11 per cent, range 10), France (16(8) per cent, median 15 per cent, range 31), the United States (12(7) per cent, median 10 per cent, range 27), Great Britain

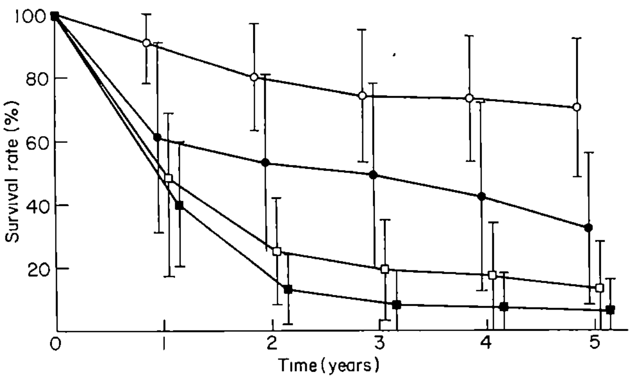

Figure 1 *Survival rate after resection according to stage (IUCC 1978) of the oesophageal carcinoma. (Stage I,* ○, n=*739, stage II,* ●, n=*1592; stage III,* □, n=*2995; stage IV,* ■, n=*1392)*

(16(13) per cent, median 10 per cent, range 24) and Germany (21(8) per cent, median 21 per cent, range 24). Since representative data on incidence, operability rates and resectability rates were not available from these countries, interpretation of these findings was difficult.

On careful comparison, it appeared that, apart from some minor details, preoperative preparation, operative techniques and post-operative therapy were almost identical internationally. This seemed to indicate that incidence and patient selection, together with the operative skills of the surgeon, were key factors determining mortality. In an endemic region, e.g. Henan-Province of China, with a screening program for oesophageal carcinoma the hospital mortality rate was low[47,129,139,144] compared with Hong Kong where even an experienced surgeon like Ong[88] had to accept a mortality rate of 40 per cent for comparable periods. Most authors deny having strict selection criteria. It is peculiar, however, that a surgical group reporting the best results in one country operated on little more than 200 patients with oesophageal carcinoma during a 15-year period and cited a resectability rate of almost 90 per cent[23]. Undoubtedly the skills and experience of the surgeon are of utmost importance for good operative results. The lowest hospital mortality rates were found in papers by surgeons having large personal experience with a great number of resections[6,23,47]. Matthews *et al.*[76] showed that there was a negative correlation between the number of carcinomas resected and hospital mortality among surgeons from a particular region. Comparison between papers published over the years by individual surgeons revealed a learning curve with a decreasing incidence of complications as clinical experience increased[23,84,112,145,146]. The above-mentioned observation applied for all countries and therefore did not explain the difference in hospital mortality rates between them.

Late-results

Fifty-six (13) per cent of all resected patients survived the first, 34(12) per cent the second, 25(12) per cent the third, 21(11) per cent the fourth and 20(11) per cent the fifth year after resection. When compared with the figures collected by Earlam and Cunha-Melo (survival rate after resection: 2-year, 29 per cent; 5-year, 18 per cent) it became apparent that surgical efforts during the past decade have not substantially improved the long-term prognosis of patients with oesophageal carcinoma.

The tumour stage encountered during operation was the primary determinant of outcome (*Figure 1*) Prognosis was excellent with tumours invading the lamina propria or submucosa only, but these represented only 9 per cent of the total of 7521 resections analysable for stage-related survival rates. Thirty-two (24) per cent of the patients survived 5 years if the tumour was still confined to the muscularis propria at the time of presentation. Lymph node involvement reduced 5-year-survival rate to 13(14) per cent. Prognosis with metastatic tumours was better than expected (5-year survival rate, 6(11) per cent). This may be explained by the fact that infiltration of intra-abdominal lymph nodes by thoracic oesophageal carcinomas was classified as visceral metastases (M1/stage IV) by the 'International Union Against Cancer' (UICC) in 1978[147]. We used this classification because most authors did or their result could be translated into it. The 1987 UICC[148] scheme added infiltration of perigastric lymph nodes to the regional involvement category (N1). This was done to assist with a more realistic differentiation of patients with advanced oesophageal carcinoma[51].

If the surgeon had the impression at the time of operation, that the tumour was completely removed (curative resection), 3-year and 5-year survival rates were 33(13) per cent and 23(7) per cent, respectively. Following palliative resection, however, only 6(5) per cent and 2(2) per cent of patients survived for more than 3 and 5 years respectively. 'Cleaning' resections to reduce the tumour mass were noted in two reports[10,23] to have a 2-year survival rate of 11·5 per cent and 9·1 per cent respectively. Because of its low hospital mortality rate (6·3 per cent and zero per cent), the authors reported excellent palliative results from this procedure with a four to six fold increase in survival time when compared to the natural course of the disease.

Although series with both squamous cell and adenocarcinomas reported a somewhat lower 5-year survival rate (18(13) per cent, compared with those including only squamous cell carcinomas (24(21) per cent), no clear evidence could be found regarding whether histological type, grading or localization of the tumour had any effect on long-term results.

Existing data did not indicate that any particular operative technique was superior with respect to long-term survival. Survival rates were almost identical if a right or left transthoracic resection or a blunt dissection was used (*Figure 2*). This also applied to the extent of lymph nodes dissection (*Figure 3*). Survival rates in reports in which authors stated that great efforts were made to dissect systematically and completely all nodes as part of the resection procedure was not significantly better than other studies. Only *en-bloc* resections showed a significantly better long-term prognosis. Analysing some of the reports[111,112,149,150] one gets the impression that this method was primarily used in patients without any risk factors and low-stage tumours. If at all, only a small number of patients with a carcinoma confined to the oesophagus and less than five regional lymph nodes involved may really benefit from this quite extensive and straining procedure.

Adjuvant treatment methods

One key to better results in the surgical treatment of oesophageal carcinoma lies in early diagnosis and resection. However, in most countries the incidence is low and mass screening successfully demonstrated in China by balloon

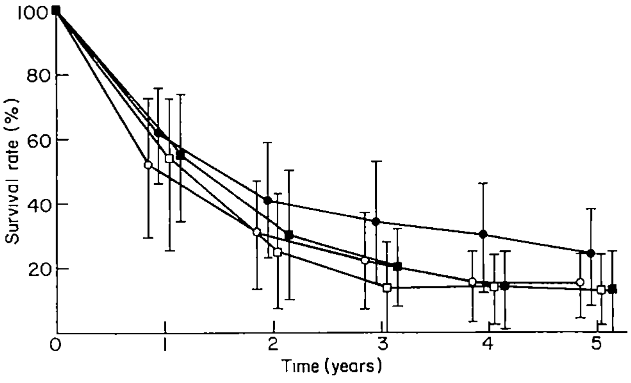

Figure 2 *Suvival rate according to the type of resection.* (○, *right transthoracic resection with intrathoracic anastomosis,* n=*3410,* ●, *right transthoracic resection with cervical anastomosis,* n=*5039,* □, *left transthoracic resection with intrathoracic anastomosis,* n=*4161,* ■, *blunt dissection,* n=*1402*

cytology[47,144] is either beyond the tolerance level of most Western populations or not cost-efficient, if conventional methods are used. Enlarging the extent of surgical excision achieved limited success in only a small group of patients. Therefore, the second best option might be multi-modality therapy because it best addresses the pathobiological behaviour of oesophageal carcinoma.

Adjuvant radiotherapy

Preoperative radiotherapy was studied experimentally and clinically by Goodner[151], Doggett et al [152] and Nakyama and Kinoshita[153] 20 years ago. Many regimens, from short-term concentrated (20 Gy in 4–5 days) to long-term fractionated radiation (60 Gy in 4–5 weeks) were used. Radiation fields always included the posterior mediastinum, but radiation of the neck, the supraclavicular regions and the epigastric triangle were optional. It was claimed that preoperative radiotherapy would.

(1) Reduce bulky carcinomas to a resectable size.

(2) Avoid the spread of viable tumour cells during the operative procedure in order to reduce the likelihood of distant metastatic spread.

(3) Destroy microscopic nests of tumour cells and tumour invasion into adjacent structures not accessible to surgical resection.

These effects were assumed to be the reason for an improvement in long-term survival found in uncontrolled trials. Subsequently, three prospective randomized trials of preoperative radiotherapy have been conducted and a fourth was prematurely terminated (*Table 5*). Preoperative complications in one trial included two cases of mediastinitis, one serious episode of oesophagitis, and one lethal bleeding episode[35]. Radiotherapy neither made the resection more difficult nor added to hospital mortality or postoperative complications. All studies failed to demonstrate a significant improvement in resectability.

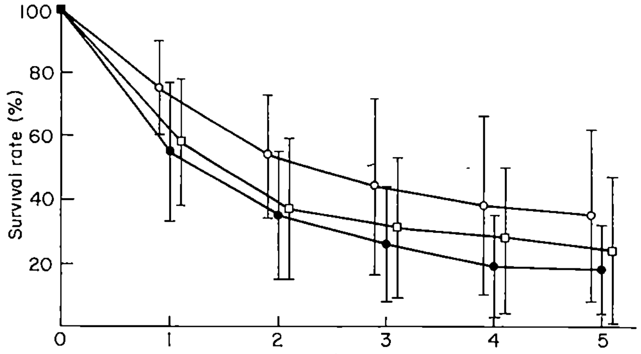

Figure 3 *Survival rate according to the extent of lymp node dissection.* ○, *en-bloc dissection,* n=*346;* ●, *conventional resection without extensive lymph node dissection,* n=*13 641;* □, *resection with extensive systematic lymph node dissection,* n=*4312)*

Although three European studies[35,155,156] did not show an improvement in long-term survival, a Chinese group[154] reported significantly higher 3- and 5-year survival rates after preoperative radiation. Unfortunately, the author did not give a detailed description of the design of the study and how patients were selected, making a critical analysis of this paper impossible. Gigoux *et al.*[35] final statement concerning the large E.O.R.T.C. trial was, '... there is no argument to recommend preoperative radiation as a routine procedure. This approach could be beneficial to carefully selected patients, but the question is whether identical results could not be obtained by radiation alone in those patients'.

It remains unclear why this theoretically and experimentally well-founded concept failed in clinical practice. Promotion of intramural lymphatic invasion and an increase in abdominal lymph node metastases in before operation-irradiated patients has been observed[157], but the relevance of these findings needs further investigation.

A Japanese multi-centre study[50] prospectively compared pre- and postoperative radiotherapy (30 Gy and 24 Gy) with postoperative radiotherapy (30 Gy) alone. A non-evaluable rate of 43·3 per cent in 364 recruited cases renders the interpretation of the result difficult. Nevertheless the group receiving postoperative radiation only showed significantly higher 5-year survival rates indicating that postoperative rather than preoperative radiotherapy may improve long-term survival. This trial supports results from five retrospective studies (*Table 6*) in which significantly longer survival was achieved with postoperative radiotherapy compared with non-irradiated historical controls. Since in the past most uncontrolled studies of preoperative radiotherapy had also reported an improvement in long-term survival, one must await statistically adequate testing of postoperative radiotherapy in the future to draw firm conclusions.

Adjuvant chemotherapy

Treatment with preoperative chemotherapy alone or in combination with radiotherapy is based on the following considerations[158]: Several post-mortem studies have demonstrated diffuse spread of the carcinoma in some of the patients who died shortly after resection had been performed. Therefore a systemic approach to the problem using chemotherapy seems reasonable. Preoperative chemotherapy proved to be superior to postoperative treatment in animal experiments. When metastatic tumour burden is low, preoperative chemotherapy

Table 5 *Preoperative radiotherapy in oesophageal cancer results of prospective randomized trials*

First author (reference)	Patient's group	*n*	PRRT	No of resections	Survival rate (%) Year				
					1	2	3	4	5
Gignoux[35]	R	102	33 Gy	75 (19)	65	47	37	28	20
	C	106		87 (17)	65	48	28	19	14
				n.s n.s			n.s.		
Huang[154]	R	83	40 Gy	79 (3)	61		51		46
	C	77		69 (3)	70		44		25
				n.s. n s			s.		
Husemann[155]	R	21	30 Gy	21 (9)	median 5·5 months				
	C	16		16 (5)	median 6·2 months				
				n s n s.			n.s		
Launois[156]	R	67	−45 Gy	47 (13)	46	21	14	14	10
	C	57		33 (7)	50	34	22	11	11
				n.s n.s.			n.s		

Values in parentheses are percentage hospital mortality rates. PRRT, preoperative radiotherapy used, R, PRRT-group; C, control group, n.s., not significant, s., significant might reduce the probability of spontaneous drug resistance and allow *in vivo* assessment of the effect of the applied chemotherapeutic agent. Since some substances have cytotoxic as well as radiosensitizing properties, a combination of chemotherapy and radiotherapy may be optimal to control regional tumour growth and to destroy systemic micrometastases.

Table 6 *Postoperative radiotherapy in oesophageal cancer· results of retrospective trials*

First author (reference)	Patient's group	*n*	PORT	Survival rate (%) Year 1	2	3	4	5
Abo[5]	C	96	–	37				10
	R	59	50 Gy	61				29
						s.		
Baulieux[10]	C	50	–	44	33			7
	R	86	45–50 Gy	59	27			15
						s.		
Hankins[43] (stage III)	C	23	–	22	8	0		
	R	25	55–60 Gy	41	14	13	13	
						s.		
Kasai[58] (stage I+II)	C	42	–	86	83	66	66	64
	R	45	50–60 Gy	93	85	81	79	71
						s.		
(stage III)	C	31	–	58	7	0		
	R	14	50–60 Gy	51	31	25	23	23
						s.		
Tanaka[119]	C	46	–	71	45	36	32	29
	R	58	40–50 Gy	49	31	19	19	19
						s.		

PORT, postoperative radiotherapy used; C, control group, R, PORT-group; s, significant

Among 11 prospective trials (*Table 7*) on pre- and/or postoperative chemotherapy only one included a group who underwent surgical resection alone[165]. Highest response rates were reported for combinations including cisplatin and 5-fluorouracil. However, extent of response was defined in many ways, data from different studies are not always comparable.

Toxic side effects of chemotherapy, depending on the drugs and dosages used, are encountered frequently and appear serious at least to a surgeon's simple eye. To list them all is beyond the scope of this review.

The chance that a patient's tumour would be resectable was not increased by preoperative chemotherapy. Only a few authors reported long-term follow-up data and these are difficult to interpret, since resections and palliative procedures were not evaluated separately. There is no evidence that preoperative chemotherapy substantially improved long-term prognosis. Some studies showed that certain patients who have limited disease will respond extremely well to chemotherapy. These patients survive longer than the rest of the identically treated collective patients[161,163,166] or as one study showed longer than patients treated by surgical resection alone[165].

Response rates following combined preoperative chemotherapy and radiotherapy were substantially higher than those after chemotherapy only. However, resectability was not increased (*Table 8*). Postoperative mortality after multimodal therapy was substantial if one considers that all studies have been performed in the past decade. Only one author[155] compared patients treated by surgery alone with a group receiving bleomycin and irradiation (30 Gy) before operation. Mortality rate was 16 per cent higher in the combined treatment group whereas median survival times were similar after a very short follow-up period. Franklin *et al.*[171] reported 1-year to 3-year survival rates for combined therapy in patients with stage I, II or III carcinomas to be 60, 38, and 29 per cent, respectively. There is no difference between their results and those reported in most studies not using adjuvant therapy Poplin *et al.*[99] reported 18 complete remissions in 113 patients receiving 30 Gy, cisplatin and 5-fluorouracil before operation.

Table 7 *Preoperative chemotherapy in oesophageal cancer· results of prospective and prospective randomized trials*

First author (reference)	PRCT	No. of patients	RR (%)	RER (%)	Median months	Survival rate (%) Year 1	2	3	4
Bains[159]	DDP, VDS, BLEO	34	65	82 (7)	19	58	44		
Bedikian[160]	DDP, 5-FU, AM	26	65	85 (9)					
Carey[161]	DDP, 5-FU	24	76	79 (0)					
(responder					20	48	48)		
(non-responder					7	20)			
						s.			
Coonley[162]	DDP, BLEO	34	14	76 (19)	10	44	12	8	8
Forastiere[163]	DDP, VDS, MGAB	29	45	93 (0)	14				
(responder						91	42	29)	
(non-responder						42	21	21)	
						s.			
Kelsen[164]	DDP, VDS, MGAG	14	42	86 (8)	26				
Roth[165]*	DDP, VDS, BLEO	19	47	(11)	9	49	25	25	
		20		(0)	9	41	14	5	
					n.s	n.s.			
Schlag[166]	DDP, VDS, BLEO	42	41	90 (11)	15	54	25		
(responder						93)			
(non-responder						50)			
						s.			
Shields[167]	DDP, 5-FU	17	76	35 (0)					
Spaulding[168]	DDP, BLEO, VBL	7	43	100 (0)					
Spielman[169]	DDP, VDS, CP	27	35	78 (17)	15				

Values in parentheses are percentage hospital mortality rate after resection. PRCT, preoperative chemotherapy used; RR, response rate, RER, resection rate; * prospective randomized trial, DDP, cisplatin; VDS, vindesine; BLEO, bleomycin; 5-FU, 5-fluorouracil; AM, adriamycin; MGAG, methylglyoxal bisguanylhydrazone, VBL, vinblastine, CP, cyclophosphamide; n.s., not significant; s , significant

Table 8 *Preoperative chemotherapy and radiation therapy in oesophageal cancer. results of prospective and prospective randomized trials*

First author (reference)	PRCT/PRRT	No of patients	RR (%)	RER (%)	Median months	Survival rate (%) . Year 1	2	3
Andersen[170]*	35 Gy	59		47	7		19	
	BLEO, 30 Gy	65		54	6		25	
					n s.		n.s.	
Franklin[171]	MITO, 5-FU, 30 Gy	30		77 (30)	12			
(Stage I–III		18				60	38	29)
Husemann[155]*	–	27		100 (31)	6			
	BLEO, 30 Gy	23	45	100 (47)	5			
					n.s.			
Iizuka[52]*	BLEO, 30 Gy	79	56	100 (11)		65		
	5-FU, 30 Gy	92	62	100 (5)		65		
						n.s.		
Leichmann[68]	DDP, 5-FU, 20 Gy	21		71 (27)	24			
Mahal[172]	DDP, AM, 40 Gy	16	94	19 (100)				
Mannel[74]*	BLEO, 20 Gy	15		100 (46)				
	20 Gy	22		100 (0)				
Parker[92]	–	12		67 (25)				25
	MITO, 5-FU, 30 Gy	43		72 (10)				26
								n.s.
Poplin[99]	DDP, 5-FU, 30 Gy	113	40	44 (17)				
('complete remissions'		18			32	84	67	45)
Popp[173]	DDP, 5-FU, VCR, 30 Gy	27	82	100 (10)	13		36	
Steiger[174]	DDP, (MITO), 5-FU, 30 Gy	48		49 (11)		68		

Values in parentheses are percentage hospital mortality rate after resection. PRCT/PRRT, preoperative chemotherapy and radiation therapy used; RR, response rate; RER, resection rate, * prospective randomized trial; † trial terminated because of high mortality in the bleomycin group; BLEO, bleomycin; MITO, mitomycin; 5-FU, 5-fluorouracil; DDP, cisplatin; AM, adriamycin, VCR, vincristine; n.s., not significant

The late results in this small subgroup were excellent; 84 per cent of the responders survived 1 year, 67 per cent two years and 45 per cent 3 years, respectively.

Non-resectional procedures

Twenty four authors communicated their experiences with 1150 bypass procedures and 13 authors reported on operative ($n=906$) or endoscopic ($n=1729$) implantation of endoprostheses. Postoperative complications and hospital mortality rates after procedures using the stomach, small intestine or colon to bypass an unresectable tumour were very high (71(27) per cent and 28(14) per cent, respectively). Median survival was 6(3) months. Since the postoperative hospitalization was approximately 4–6 weeks[102], the question whether bypass procedures are beneficial remains controversial. Operative implantation of endoprostheses has been replaced by endoscopic placement during recent years because it is more convenient for both patient and surgeon. Real hospital mortality rates cannot be assessed for endoscopic placement, since most authors reported only 'treatment-related mortality' (10(4) per cent). Following operative implantation of endoprostheses, 21(9) per cent of the patients died while still in hospital. The median survival time was 5(3) months.

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Percutaneous endoscopic gastrostomy

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The many variations of surgical gastrostomy for nutritional support or for long-term gastric decompression all have a significant morbidity and mortality. An 'incisionless' technique under local anaesthesia, namely percutaneous endoscopic gastrostomy, was described in 1980. A review of the literature shows that the percutaneous technique is safer for the patient, easier and faster to perform and considerably cheaper than surgical gastrostomy. As the few complications usually require surgical management, percutaneous endoscopic gastrostomy should be considered a surgical technique. Few patients are unsuitable for the percutaneous endoscopic technique and this route should be considered for all patients referred for a gastrostomy.

Keywords: Percutaneous endoscopic gastrostomy, indications, complications, results, surgical gastrostomy

Gastrostomy is one of the oldest abdominal operations in continuous use today[1] and entails the operative creation of a fistulous tract between the stomach and the abdominal surface; many variations of the technique have been described[2]. However, one of the most significant advances in the creation of a gastrostomy must be the percutaneous endoscopic technique described in 1980 by Gauderer *et al.*[3]. Gauderer, a paediatric surgeon, was motivated by the large numbers of paediatric patients (usually with brain damage) who required a feeding gastrostomy. Many of these children have major risk factors for general anaesthesia such as contractures, seizure disorders and increased intra-abdominal pressure. In common with adult patients who require gastrostomy they were usually malnourished.

Gauderer and Ponsky performed the first 'incisionless' gastrostomy in 1979 using a home-made kit manufactured from a 16Fr Pezzer catheter. Subsequent modifications of the technique of percutaneous endoscopic gastrostomy have been accompanied by the production of commercial kits. It is now an eminently feasible technique which should be considered in all patients who are referred to the surgeon for the sole purpose of placing a feeding gastrostomy[1,4].

Recent modifications also allow the placement of the tip of the tube in the duodenum or jejunum in patients with gastro-oesophageal reflux in whom aspiration pneumonitis is a potential problem. The technique is widely practised and reported in North America but there have been few reports in the European literature.

Indications

The indications for gastrostomy fall into two categories, namely nutritional support and long-term gastric decompression.

Nutritional support

Gastrostomy is a well recognized and satisfactory method of providing long-term enteral nutrition[5]. While there have been impressive advances in the use of total parenteral nutrition in the management of the severely ill patient, enteral nutrition, if appropriate, is metabolically more effective[6] Furthermore parenteral nutrition has life threatening complications, is expensive, and is inappropriate for a patient with a functioning gastrointestinal tract.

Fine-bore nasoenteric tube feeding remains the route of choice for patients unable to eat normally and who are expected to require short-term nutritional support. It is difficult to define exactly what short-term means in this context and with improvement in percutaneous endoscopic gastrostomy techniques and catheters the place of nasoenteric feeding may well become more restricted.

Although nasoenteric tube feeding is simple to initiate and is arguably less invasive than percutaneous endoscopic gastrostomy, there are some disadvantages associated with its use. The constant, visible presence of a tube makes even fine-bore tube feeding unacceptable to many patients for more than a few days, especially outside the hospital environment. One solution is for patients to learn to perform intermittent self-intubation. However, this may be technically and/or aesthetically beyond the capabilities of some. In patients with abnormal gag or swallowing reflexes there is a risk of misplacement of the tube, or overspill of stomach contents, which may lead to aspiration pneumonitis. There are numerous other complications of nasoenteric tube feeding, especially if it is required for prolonged periods[5]. Such patients should be considered for a gastrostomy or enterostomy[7,8]. *Table 1* gives examples of conditions which may be suitable for percutaneous gastrostomy.

Long-term gastric decompression

Percutaneous endoscopic gastrostomy has been used successfully in patients who require prolonged gastrointestinal decompression[9]. In a small series of nine patients, gastric decompression and elimination of the need for nasogastric intubation was achieved in all. Three patients were discharged home and continued to use the gastrostomy for gastric decompression for the remainder of their lives (2–24 months). An added advantage is the fact that the volume of gastrostomy drainage is less than nasogastric aspirate[10]. Many patients with abdominal malignancy, who may only have a limited lifespan, require gastric decompression. Some may be suitable for percutaneous endoscopic gastrostomy and may gain an improvement in the quality of their life with a percutaneous endoscopic gastrostomy instead of a nasogastric tube[11].

Contraindications

Contraindications are few but patients should be carefully

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Table 1 *Examples of conditions in which percutaneous endoscopic gastrostomy may be appropriate*

- Neurological disorders
  - Hemiplegia
  - Motor neurone disease (bulbar palsy)
  - Brain injury (trauma or surgical)
  - Other neurological causes of difficulties in swallowing
- Head, neck and oesophageal malignancies
  - (Especially those undergoing curative or palliative radiotherapy where initial oedema may increase dysphagia.)
- Oesophageal perforation
  - Conservative treatment of spontaneous perforation
  - Some postoperative leaks
- Supplemental feeding
  - Cystic fibrosis
  - Short bowel syndrome
  - Scleroderma
  - Nocturnal hypoglycaemia
- Confusional states in which feeding is required
  - (A gastrostomy may be far better tolerated than a nasoenteric tube.)

selected. There is little value in using percutaneous endoscopic gastrostomy in a patient whose life expectancy is only a few days. The presence of a normally functioning intestine capable of absorbing the infused nutrients is essential.

The procedure should be avoided in patients with sepsis or massive ascites and in those undergoing peritoneal dialysis[12]. Previous abdominal surgery is not a contraindication[13] provided extra caution is taken and the inflated stomach can be approximated to the anterior abdominal wall. Previous gastric resection is not a contraindication in itself but is often responsible for an inability to perform the procedure.

An oesophageal stricture is not a contraindication as a paediatric gastroscope may be used or the stricture may be dilated[14]. Relative contraindications are coagulation disorders and Crohn's disease with intestinal fistula.

Technique

The original description of the technique involved pulling the gastrostomy catheter down the oesophagus, into the stomach, and out through the abdominal wall (the 'pull' method)[3]. This is the most widely used technique but additional methods have been described. One of these pushes the tube into place over a guidewire (the 'push' method) and is a modification of a technique described by Sacks and colleagues[15]. They described a radiological technique for percutaneous insertion of a gastrostomy in the dog that did not require endoscopy. This radiological technique has been adapted and developed in humans by Ho and colleagues[16] and will be discussed later.

The third method (the 'introducer' method) places a Foley catheter into the stomach through a split-sheath introducer. This is a modification of the Seldinger technique similar to that used for the insertion of central venous catheters[17].

In all methods two operators are required. One dose of a broad spectrum antibiotic should be given as prophylaxis before the procedure. The patient is prepared as for upper gastrointestinal endoscopy. It is necessary to position the patient supine during the procedure, and so it is essential to have an additional assistant to apply suction to the posterior pharynx to prevent aspiration of secretions.

Intravenous sedation and posterior pharyngeal anaesthesia with lignocaine spray are administered and the endoscope is passed into the stomach. This part of the procedure may be performed with the patient in the left lateral position, but it is then necessary to turn the patient into the supine position. After inspection of the stomach and the duodenum, the stomach is fully inflated with air. The endoscopist directs the tip of the gastroscope towards the anterior abdominal wall and the room lights are dimmed. The abdominal operator observes the abdominal wall, looking for an area of transillumination. This indicates the site at which the stomach and the abdominal wall are in close contact without interposed tissue. Finger pressure at this site will cause a definite indentation in the gastric wall which can be seen by the endoscopist.

A site is selected, usually in the left upper quadrant away from the costal margin. The area is cleaned with a colourless skin preparation (dark solutions may obscure the transillumination).

The chosen site is infiltrated with local anaesthetic through all layers down to the gastric lumen. Care must be taken to avoid the epigastric vessels, which may be visible in a thin patient on transillumination. A small incision, just larger than the external diameter of the gastrostomy tube, is made in the anaesthetized skin with a scalpel. The remainder of the procedure varies with the method used.

Pull method

The endoscopist opens a polypectomy snare over the proposed site on the inner wall of the stomach (*Figure 1*). An intravenous type cannula (this is supplied with the commercial kits) is thrust through the apposed abdominal and gastric walls into the waiting snare loop. The snare is then tightened around the cannula and the metal needle is removed. A strong suture is passed through the cannula and the snare is slid off the cannula to grasp the suture (*Figure 1*). The scope, snare and suture are then pulled up through the oesophagus and out of the mouth. The other end of the suture is retained by the abdominal operator. The suture is then tied to the tapered end of the gastrostomy tube (*Figure 2*). The abdominal operator pulls the tube through the oesophagus and stomach until the tip engages in the cannula. The cannula and tube are withdrawn together through the anterior abdominal wall until the gastric retainer rests against the inner wall of the stomach (*Figure 3*). This apposes the stomach and the anterior abdominal wall The endoscopist passes the scope once more and ensures that the gastric retainer lies just against the gastric wall. Excessive tension on the tube should be avoided as this may produce ischaemia and necrosis, which in turn may lead to infection or extrusion of the tube. The external portion of the tube is cut to size and the adaptor is fitted according to the manufacturer's instructions.

This is the originally described method[3] and is the most widely used and reported. One disadvantage is the possibility that the suture may break or come undone. This was a problem with the initial home-made kits but this complication has been practically eliminated with the newer commercial kits. A further disadvantage is that a repeat gastroscopy is required for removal of the tube at the end of treatment.

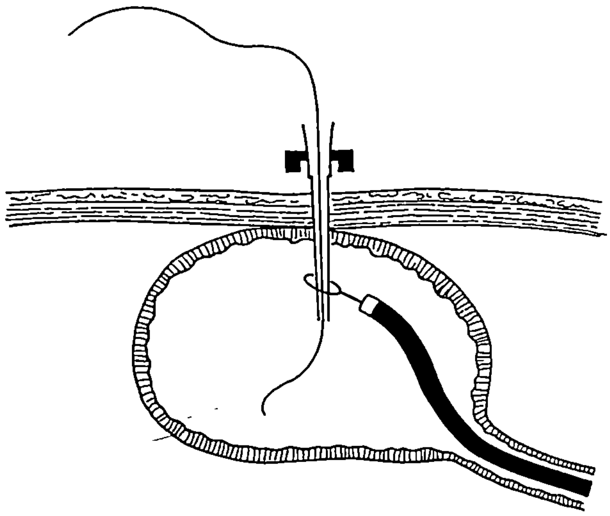

Figure 1 *A strong suture is passed through a cannula which has been thrust through a transilluminated area into the inflated stomach. The endoscopic snare encircles the cannula. When the suture is visualized the snare is slid off the cannula to grasp the suture*

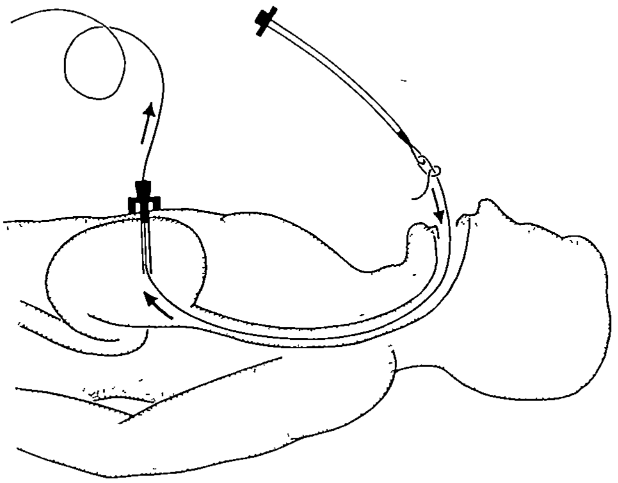

Figure 2 *Gastroscope, snare and suture have been withdrawn and the suture is tied firmly to the tapered end of the gastrostomy tube Traction is applied to the suture and the tube is pulled down the oesophagus into the stomach until it engages the cannula*

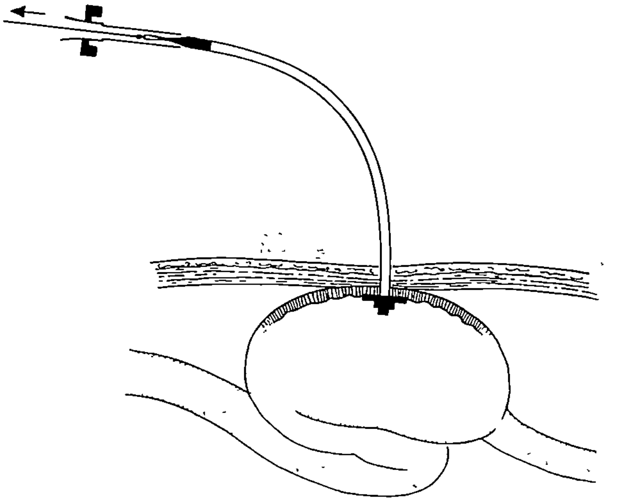

Figure 3 *Traction is continued until the gastric retainer engages the stomach wall. The tube is now in place. The external portion is cut to size and the adaptor fitted according to the manufacturer's instructions*

Push method

In this method a flexible wire is passed through the cannula into the opened polypectomy snare. The wire is pulled out of the patient's mouth while one end is held by the abdominal operator. A specially designed long firm tube, with a tapered end, is pushed over the wire until it engages the cannula. The tube and cannula are then pushed through the abdominal wall (*Figure 4*). The wire is withdrawn from the abdominal end. The tube is cut to size and the connectors are attached. An endoscopic check of the position and tension of the gastric retainer is recommended. An advantage of this technique is that the operator has full control over the tube at all times. Furthermore there are none of the problems associated with a suture.

The disadvantages are that it is theoretically possible to damage stomach, oesophageal and pharyngeal tissues, though this has not, to our knowledge, been reported. A repeat gastroscopy is required for removal of the tube.

Introducer method

This technique is based on the methods developed for the insertion of central venous catheters and pacemaker wires. A guidewire is passed through a cannula (or a metal needle) into the stomach. A tapered introducer with a split-sheath over it is passed over the guidewire. The introducer and guidewire are removed and a small (14Fr) Foley catheter or similar type gastrostomy tube with an inflatable balloon is inserted through the split-sheath. The balloon is inflated and the split sheath is peeled apart. A second endoscopy is not required.

It has been claimed that the risk of infection is less as this technique avoids the need to pull, or push, the tube through the mouth and oesophagus[18]. A definite advantage is that the tube is easily removed by deflating the balloon and does not require an endoscopic procedure for either changing the tube or at the end of treatment.

A disadvantage of this method is the fact that the openings in the abdominal wall and stomach are bigger than the gastrostomy tube. This can result in leakage of gastric contents. Furthermore early displacement can occur if the balloon deflates. Panzer *et al.*[19] reported displacement in 6 out of 26 patients and four required a further endoscopy to replace the tube.

Complications

The complications of percutaneous endoscopic gastrostomy can be divided into insertion complications and 'in-use' complications.

Insertion complications include complications of endoscopy, misplacement of the tube and infection of the stomal site. Failure to perform percutaneous endoscopic gastrostomy is unusual and Ponsky *et al.*[20] reported an initial success rate of 100 per cent in 150 procedures. This probably reflected careful selection of patients with the exclusion of patients likely to prove difficult, such as patients who had previous gastric surgery or were very obese. Relaxation of selection criteria has inevitably led to an increase in the failure rate. Recent series report a failure rate of about 5 per cent[4,12,21]. The usual reason for failure is the inability to appose the stomach to the anterior abdominal wall because of previous surgery or gross obesity[4,12,21].

Complications of an endoscopy are mainly pulmonary and can be fatal. Misplacement of the tube with damage to adjacent viscera should be rare but is more likely if there has been previous upper abdominal surgery. Gastrocolic fistula has, to our knowledge, been reported on two occasions[1]. Theoretically this could occur at insertion, or by erosion of the tube into the colon.

Infection at the exit site is relatively common. Jain *et al.*[22] have reported that administration of a cephalosporin reduces

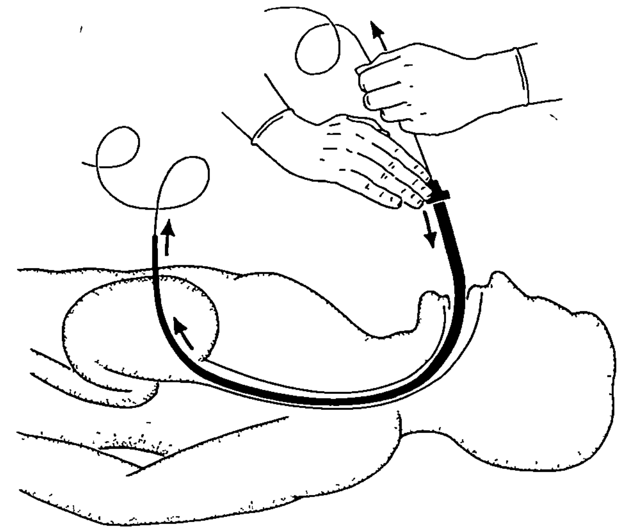

Figure 4 *Push method a long flexible guidewire has been passed into the stomach and retrieved using the endoscopy snare. The long tapered tube is pushed over the wire until the end can be grasped by the abdominal operator, who then pulls the tube into place*

peristomal wound infections from 28·6 to 7·4 per cent. However, Jonas *et al.*[23] found that use of antibiotics did not reduce the 30 per cent incidence rate of infection seen without antibiotics. Part of the problem is the exact definition of a peristomal infection. It is common to have some peristomal leakage and culture of this fluid will usually demonstrate the presence of organisms. However peristomal infection should only be diagnosed if there are clinical features of infection, such as pain or peristomal cellulitis. Using these criteria Foutch *et al.*[24] reported no infection in 150 consecutive procedures in patients given prophylactic antibiotics The balance of opinion is in favour of prophylactic antibiotics[1,4,17,21,24].

It is also recommended that the skin exit site should be slightly larger than the gastrostomy tube to allow any wound fluid or secretions to drain externally[1,3,21,24].

Fatal necrotizing fasciitis has been reported as a complication in a diabetic woman[25]. It was suggested that a contributing factor in this case was a very small incision which did not allow adequate drainage to occur.

Mechanical in-use complications of the tube include blockage, fracture, hub detachment and displacement. Metabolic complications include 'dumping' syndrome and diarrhoea and are more common when the tip of the tube lies in the duodenum or jejunum.

Gastrostomy tubes of the Foley catheter type, incorporating a balloon, have been reported to cause gastric outlet obstruction[26,27] The usual presentation is abdominal pain, vomiting and discharge around the catheter in a patient with a gastrostomy. Traction on the catheter to appose the balloon to the stomach wall resolves the problem.

Gastro-oesophageal reflux of the feed can pose problems and may lead to aspiration pneumonia. Reflux can be reduced by duodenal intubation. Most of the modern kits are designed so that a smaller tube may be passed through the gastrostomy tube *in situ*. This smaller tube can then be guided endoscopically into the duodenum. However, a tube in the duodenum is more likely to cause diarrhoea and other gastrointestinal effects, particularly with bolus feeding or rapid infusion rates[11].

Cumulative data from the literature shows that the overall procedure related morbidity rate is of the order of 9·7 per cent[1,4,17,18,28–31].

Our own experience in 13 patients, using either the pull or push method, has been very encouraging. To date we have had one failure in a patient who had a previous subtotal gastrectomy. All were adults with a median age of 63 years (range 23–84 years). The indications were hemiplegia (4 patients), head injury (4 patients), motor neurone disease with bulbar palsy (2 patients), pharyngeal tumour (1 patient), nocturnal hypoglycaemia (1 patient) and scleroderma (1 patient). The median in-use time has been 176 days (range 21–320 days). Three gastrostomy tubes have been removed at the end of treatment and four are still functioning Six patients have died 21–320 days postinsertion of the gastrostomy. There has been one peristomal infection which resolved on antibiotic treatment Careful instruction in the care of the tube, particularly with regard to regular flushing, has resulted in surprisingly few mechanical complications when in use. Catheter obstruction has occurred once but the tube was cleared with a metal guidewire. Damage to the hub requiring repair or replacement is common with long-term usage and has occurred in five patients.

Comparison of percutaneous and surgical gastrostomy

There are no randomized controlled trials which compare percutaneous with conventional gastrostomy. The majority of studies have used historical controls or procedures performed concurrently.

A review by Foutch and colleagues[24] of recent series found little difference in the morbidity rate associated with either technique However, more than 50 per cent of surgically treated patients in five recent series received general anaesthesia. Surgical patients had more pulmonary problems than were found after percutaneous gastrostomy (2 *versus* 0·6 per cent). Earlier commencement of feeding is possible in patients who have undergone percutaneous insertion One important observation was that the cost of a surgical gastrostomy is two to three times greater[1,4,24,30,31] Two recent studies[30,31] compared surgical gastrostomy with percutaneous gastrostomy performed concurrently in the same institution Gupta *et al.*[30] compared the insertion time, time from gastrostomy to initiation of feeding and major and minor complication rate in 50 percutaneous gastrostomies and 60 consecutive surgical gastrostomies performed during the same period. The two groups of patients were similar Insertion time (40 min for percutaneous gastrostomy compared with 57 min for surgery) and time to initiation of feeding (1·5 days and 4 days respectively) were significantly less in the percutaneous gastrostomy group. Procedure-related mortality rate was 2 per cent in the percutaneous group compared with 7 per cent in the surgical group Major and minor complication rates were 2 and 12 per cent respectively after percutaneous gastrostomy, compared with the 10 and 23 per cent respectively after surgery.

Grant[31] compared the results of percutaneous gastrostomy ($n=125$) with those of the Stamm surgical gastrostomy ($n=88$) He found that percutaneous insertion reduced operative time (50 *versus* 96 min) and the necessity for general anaesthesia (13 compared with 64 per cent). Insertion by percutaneous means was $1000 dollars cheaper and recovery time before feeding was shorter at 1·8 compared with 3·4 days for surgery Insertion complications were significantly reduced with percutaneous insertion (8·8 compared with 23·9 per cent for surgery).

Grant[31] makes the important observation that, as most complications require surgical management, it is likely that these would be most quickly recognized and expeditiously handled by the surgeon. He concludes that percutaneous gastrostomy is best performed by surgeons rather than by gastrointestinal endoscopists.

The results of non-endoscopic percutaneous procedures have also been encouraging[16,32]. Ho and colleagues[16] compared mortality and morbidity rates in a retrospective series of 133 patients who had percutaneous non-endoscopic gastrostomy (radiological technique) with 100 patients who had surgical gastrostomy. There were significantly fewer major and minor complications with percutaneous non-endoscopic gastrostomy. Displacement of the catheter with intraperitoneal nutrient infusion occurred in two of the first 73 percutaneous procedures but was not recorded in the subsequent 50. Similarly Gray *et al.*[32] recorded five early dislodgements following placement of 72 gastrostomies with resulting loss of enteral access. Catheter displacement is more likely in radiologically placed percutaneous gastrostomy, as fixation of the tube is mainly by extra-abdominal mechanisms It would seem safer to insert a gastrostomy tube under direct vision using an endoscope but safe placement by a skilled radiologist is certainly possible[16,32].

Complication rates in children have been similar to those in adults, and most have been of a minor nature[12]. Indeed the original technique was designed and used in children[3]. Ponsky and Gauderer[12] have performed 100 procedures, with few complications, in children as young as 1 month and as small as 2·5 kg.

The cumulative results suggest that percutaneous endoscopic gastrostomy has significantly fewer complications than surgical gastrostomy, is less expensive and less time consuming to perform. The original homemade tubes have been superseded by commercially marketed kits. Currently available kits in the UK use the pull method (Frenta, Fresenius, Runcorn, UK; Gilsdorf PEG Scientific Hospital Supplies, Liverpool, UK) or the push method (Flexiflo PEG Set, Abbott Laboratories, Maidenhead, UK)) Complete kits cost from £20–100

The surgeon, faced with a patient who requires a gastrostomy, should consider the percutaneous endoscopic route before embarking on surgical gastrostomy.

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Surgical pathology of HIV infection: lessons from Africa

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Human immunodeficiency virus has resulted in a major change in the presentation and behaviour of certain common diseases in Africa. This review descibes some of the important changes and discusses the implications for management

Keywords: HIV infection, AIDS, sepsis, surgical tuberculosis, Kaposi's sarcoma, blood transfusion

Very few papers have described the surgical consequences of infections with the human immunodeficiency virus (HIV) in the West[1,2], and in Africa accounts of HIV-related pathology have been confined almost entirely to informal occasions when surgeons drink together and tell stories of surgical adventure. Whenever I travel to meetings of the Association of Surgeons of East Africa, my friends seize the opportunity to recount their HIV-related disasters or triumphs. In countries where seroprevalence rates among urban adults range from 5 to 20 per cent or more[3,4] the practice of surgery may be potentially hazardous, but it is also exceedingly interesting My purpose in this paper is to share some of these discoveries.

Methods and sources

I work in Zambia which is south of the equator, bordered to the north by Zaire and Tanzania, to the south by Mozambique, Zimbabwe and Namibia, to the west by Angola and to the east by Malawi. In 1986 the population was 7·0 million. About 45 per cent of our people are less than 15 years old, so that the population structure is very different from that of the West, and unlike neighbouring countries, 50 per cent of Zambians live in cities.

Since 1983, when a change in the presentation of Kaposi's sarcoma[5] drew attention to HIV infections in Zambia, we have seen a marked increase in the prevalence of HIV-related disease. Transmission is mainly heterosexual and vertical, so that the sex ratio for disease and seropositivity is nearly equal The common opportunists are tuberculosis, candidiasis, herpes zoster, Kaposi's sarcoma, and cryptococcal meningitis.

It takes a certain critical mass of experience to recognize new presentations of old diseases and entirely new pathologies when they are embedded in the routine of familiar work. We have now begun prospective studies of specific pathologies but much of the material in this paper is descriptive or even anecdotal, although it does indicate directions needing exploration. However, there are already a few reports from Lusaka that provide quantitative information, and I shall refer to preliminary data from a survey of the surgical pathology of HIV-infections, which began in Zambia this year. We are studying patients aged 15 years or older admitted as surgical emergencies to the University Teaching Hospital (UTH), Lusaka, during four non-consecutive days, and all patients occupying surgical beds at selected rural hospitals during unannounced visits lasting 2 or 3 days. So far we have seen 58 patients admitted to UTH, and 154 patients in five other hospitals. The mean seropositivity rate for antibody (using the recombinant Wellcozyme test (Wellcozyme Diagnostics, Dartford, UK)) is 24·3 per cent, with a range from 11 per cent to 45 per cent for individual hospitals. It is disturbing to find that 15 per cent of negative tests came from patients with signs suggesting advanced HIV-related disease: clearly antigen assays on these samples will be needed to give a complete picture of HIV-related pathology in Zambia.

Themes

In Africa we are seeing changes in the presentation and behaviour of common diseases, alterations in the prevalence of some conditions, a changing pattern of complications following treatment, and the emergence of a few entirely new syndromes.

In this unfamiliar territory we recognize (so far) five landmarks:

1. An increased incidence of sepsis, arising spontaneously or as a complication of elective surgical procedures
2. An increase in surgical tuberculosis matching the increase in pulmonary tuberculosis reported from many hospitals
3. Impaired wound healing, a variety of skin lesions, and genital ulcers
4. Tumours or tumour-like conditions which are associated with or influenced to behave differently by HIV infection
5. Previously unreported pathologies.

Signs predicting infection and patient numbers

In East and Central Africa several physical signs which are strongly and consistently associated with the presence of HIV infection have become common. These are: symmetrical lymphadenopathy, distinctive scars of a maculopapular rash or of herpes zoster, oral thrush or hairy leukoplakia, the unchanging, haunted, stare of the patient with encephalopathy, and Kaposi's sarcoma of the skin or mouth. Atypical and aggressive Kaposi's sarcoma was first recognized in Zambia in 1983, occurring alongside endemic Kaposi's sarcoma[5,6]. Since then numbers of new patients with HIV-related Kaposi's sarcoma have increased exponentially.

What does this mean, in practical terms (when extrapolated to the whole range of HIV-related pathology), to already overextended health services? It corresponds to an increase, per unit time, from four to over 400 patients in less than 5 years, an increase which is the actual experience of some hospitals in East and Central Africa.

Surgical sepsis

HIV-infection predisposes patients to acquire surgical infections and, in high-incidence areas, it may be a more frequent association than diabetes. The common sites are the female genital tract, the pleural cavity, large joints, and the anorectal area. A few patients have multiple abscesses or infection in unsual sites such as the thyroid gland.

Gynaecological sepsis. In Lusaka, during 1986 and 1987, 29 of 65 patients admitted to the intensive care unit with severe sepsis of obstetric or gynaecological origin were HIV-positive (44 per cent), contrasting with 13 per cent of 70 obstetric patients admitted to the same unit without sepsis in the same period ($P < 0{\cdot}001$). The outcome of gynaecological sepsis was worse in HIV-infected patients, of whom 65 per cent died,

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compared with 42 per cent of HIV-negative patients, but this difference just failed to reach statistical significance[7]

Empyema. Throughout our region empyemas were seen regularly but infrequently in the past. In Lusaka, empyema has become such a common diagnosis that a prospective study started in April 1989 has recorded, so far, 14 new patients with this diagnosis, all of whom were seropositive for HIV antibody. These men, mostly in their thirties, presented with subacute symptoms, usually chest pain, but without fever or systemic upset. A few were known or suspected to have tuberculosis, and on several occasions pus was found on aspiration instead of the anticipated effusion. These patients had severe weight loss and other signs of advanced HIV-related disease. They were treated by intercostal tube drainage but without antibiotics. Unless there was underlying tuberculosis, the lung usually re-expanded rapidly and completely, suggesting that infection did not produce the usual fibrinous exudate or rapid fibrous organization of a limiting membrane So far, no empyema has become chronic, but the patients' general health has rarely improved and several have already died.

Septic arthritis. Septic arthritis is common in African children (alone or as a complication of haematogenous osteomylitis), but it was rare in adults, except as a consequence of penetrating injuries. Now septic arthritis is a common presentation of HIV infection in young adults who are otherwise still reasonably fit. The onset is acute, one joint (usually the knee) is affected, and the initial response to arthrotomy and antibiotics is good; but then inflammation fails to resolve and the condition becomes chronic.

The following case report illustrates some of the problems posed. A man, aged 25 years, presented in January 1988 with a 3-day history of painful swelling of one knee At arthrotomy turbid fluid containing shreds of necrotic tissue was drained and the wound was left open. After antibiotic administration and traction, secondary suture was undertaken and he left hospital 'doing well' 3 weeks later. He returned with wound breakdown after a fortnight and he has been in and out of hospital ever since Turbid effusions have been aspirated many times, he has had two 'wide' arthrotomies and a partial synovectomy undertaken by an experienced orthopaedic surgeon, but no macroscopic or histological evidence of tuberculosis has been found.

Pyogenic staphylococci remain the commonest causative organisms, with gonnococci isolated rarely. Some exudates yield a variety of *Salmonella* species or exotic bacteria.

Haematogenous osteomyelitis is very rare in immunologically normal adults, except as a complication of bone necrosis in homozygous sickle cell disease, but it does occur in HIV-infected adults, often simultaneously and symmetrically in two bones. The presenting features and behaviour of these infections are so unique that we regard HIV-related osteitis as a new entity, which I shall describe below.

Anorectal sepsis In our surgical pathology survey, eight of 48 seropositive patients had inflammatory conditions of the anorectal area, in keeping with Western experience (A. Stotter, personal communication). None of our patients practised anal intercourse, either homosexual or heterosexual.

We are wary of laying-open fistulae in HIV-positive patients, as healing may fail to occur. Similarly, I prefer to manage haemorrhoids conservatively and avoid anal dilatation or sphincterotomy as either may impair continence for frequent watery diarrhoea, a problem to which many patients will be condemned in the later stages of their disease.

Sepsis following clean elective surgery. Jellis[8], writing in *Surgery in the Tropics* recounts the bitter experience of orthopaedic surgeons: '. . we find that patients carrying HIV develop an unacceptably high level of wound sepsis after implant surgery. We would therefore avoid internal fixation whenever possible.' He and his colleague in Lusaka like to know whether or not prospective patients are seropositive before planning treatment for some fractures

In the surgical pathology survey, 13 of 48 seropositive patients were admitted to hospital for trauma, usually fractures or burns, and HIV infection was not suspected by the admitting doctors, although in some cases there were suspicious physical signs. Management decisions in these patients may be difficult.

For example, a 30-year-old man has non-union of bilateral (initially open) tibial fractures 7 months after they were sustained in a road accident, one wound healed, the other did not and a sequestrum was removed through it. The patient is unwell and has symmetrical lymphadenopathy Is it possible to clear chronic infection from his tibiae, supply bone grafts and achieve healing?

Increased incidence of late infections of prostheses. Another problem is the late infection of implanted metal, which has occurred several times in HIV-infected patients in Lusaka. In one illustrative case, a 33-year-old woman had a giant cell tumour of the upper femur resected in 1979 and replaced by a custom-made prosthesis. Postoperative recovery was uneventful, and she subsequently had three children without receiving prophylactic antibiotics and without infection. In 1989 she suffered a spontaneous abortion followed by pelvic peritonitis and then severe pain in her hip. On admission she had dislocation of the prosthesis which has now been removed; pus in the remains of the hip joint yielded *Proteus mirabilis* and *Staphylococcus epidermidis*. This woman is thin, seropositive for HIV antibodies, and gives slow and inaccurate answers to questions, showing that she has some degree of encephalopathy.

Surgical tuberculosis

We are seeing an increase in surgical tuberculosis of spine, bone, joints, and lymph nodes but not, surprisingly, of the peritoneal cavity or urogenital tract. This is happening in the context of a marked and continuing increase in the incidence of pulmonary tuberculosis in affected countries[9–11], and a clear association between this increase and infections with HIV. For example, in Lusaka during 3 months (in late 1988 and early 1989) 49 per cent of 149 new patients with confirmed pulmonary tuberculosis were seropositive by Wellcozyme recombinant ELISA, and for 19 patients with tuberculous pericardial effusion the rate was 84 per cent[12]. Surprisingly, HIV positive patients were less likely to have a positive sputum smear than their HIV negative counterparts, and more likely to have a chest radiograph showing middle and lower zone disease but sparing of the lung apices[12].

In Ndola, on the Copperbelt, there were 308 new patients with tuberculosis in 1985, 370 in 1986, 434 in 1987 and 505 in 1988, of whom 58 per cent were seropositive for HIV antibodies (M. N. Maboshe, personal communication).

Tuberculosis of the spine. Tuberculosis of the spine is now a common diagnosis in Lusaka, but in HIV-infected patients it does not respond predictably or well to antituberculous drugs. In some patients the disease appears to be of recent onset, but in others it is clearly due to reactivation of a process that had been 'healed' since childhood. In either case backache, a gibbus, and increasing paralysis may develop in a patient who is otherwise at an early stage of HIV-disease. The surgeon is then in a quandary when (as is usually the case) several weeks of anti-tuberculous drugs do not reverse the paresis. So far our orthopaedic surgeons have not attempted radical surgery for patients who are known to be HIV positive but the decision is doubly difficult because paraplegic patients who are also HIV-infected develop pressure sores of horrific size and depth very quickly[13] For tuberculosis of the spine which is not complicated by paraplegia, the Medical Research Council trials have, of course, shown that conservative treatment is better than radical surgery, except in the hands of a few very experienced operators.

Tuberculosis of bone and joint Tuberculosis of bones and joints was uncommon in Zambia, but the incidence has increased again in the last 2–3 years The patients are young adults, often in reasonably good health, who develop insidious symptoms in a single large joint, most commonly the hip or knee, although we have seen solitary examples of tuberculosis at other sites. The appearances at open biopsy are diagnostic, with extra-articular cold abscesses, pale gelatinous thickening of the synovium, purulent effusions and masses of granulation tissue which undercut and lift sequestra of joint cartilage. Unlike tuberculosis of lungs, nodes and pleura, anergic tuberculosis of bone and joints responds poorly to conservative management, and orthopaedic surgeons ask if there may be a place for aggressive surgical treatment of HIV-positive patients, combined, or course, with antituberculous drugs

Tuberculosis of lymph nodes. Ten years ago I excised for histological examination any lymph nodes which had remained palpable over a month or so, and I learned a good deal about the early stages of HIV-related illness by continuing this policy during 1984 and early 1985 Now it is unrealistic, because many patients have persistently enlarged nodes due to the reactive hyperplasia of HIV infection, but they do not need specific treatment. The lymphadenopathy of otherwise symptomless patients is symmetrical relative to the sagittal plane, and the nodes are usually 2 cm or less in diameter, firm, numerous, mobile and separate from each other. I have adopted two criteria for surgical biopsy: marked asymmetry in the distribution or size of nodes, and nodes which exceed 3 cm in average diameter.

This new policy needs testing, and in any case it still leaves a lot of nodes needing biopsy. Bem and Patil in Lusaka have passed the half-way mark in their planned study of 200 node biopsies in HIV-positive patients. So far about three-quarters of all biopsies show tuberculosis, and about 10 per cent show unexpected Kaposi's disease which is obvious macroscopically, as the sectioned node is dark red in colour. Occasionally tuberculosis and Kaposi's sarcoma co-exist in the same node. Lymphomas appear to be less common than they are in the West In this study nodes have been excised from 'every conceivable site', including the epitrochlear, infraclavicular and iliac groups

Tuberculosis of retroperitoneal nodes has been recognized on a few occasions in HIV-infected patients who presented with large masses suggesting a retroperitoneal sarcoma or lymphoma, but only after open biopsy. At least at first, treatment with antituberculous drugs was rewarding, as masses diminished in size, symptoms were relieved and general health improved.

I have seen one man with an unusual double infection of intra-abdominal nodes. He presented as an emergency with subacute peritoneal irritation, superimposed on a history of chronic distension and pain for 2 weeks. He had gross weight loss and other stigmata of HIV infection, so I suspected secondary bacterial infection of tuberculous peritonitis and began conservative treatment. Some 12 h later his signs had worsened and I did a laparotomy, finding no tubercles, and only a small quantity of clear odourless fluid in the peritoneal cavity. There were many soft discrete swellings in the mesentery and retroperitoneal tissues which ruptured as I delivered loops of bowel for inspection, releasing a thin odourless pus suggesting staphylococcal infection. The small cavities, once drained, showed no thickening of their walls to suggest chronic tuberculosis, but the pus contained innumerable acid-and-alcohol-fast bacilli and also yielded a pure culture of *Salmonella* species. The patient made an uneventful recovery from surgery and left hospital on antituberculous therapy in improving health, but returned with renewed weight loss and died about 4 months later.

Surgical subspecialities and HIV-related pathology Tuberculosis has been seen in the larynx of HIV-infected patients, mimicking carcinoma. One ear, nose and throat surgeon suspects that tuberculosis of lymphoid tissue adjacent to the Eustachian tube may be responsible for the conductive deafness which is common in these patients, and has started a prospective study of the problem. Laryngeal Kaposi's sarcoma is another new cause for hoarseness, but that diagnosis can be made on inspection, as typical dark red or purple nodules are seen on the cords.

Ophthalmic surgeons see patients with the destructive effects of herpes zoster of the ophthalmic division of the trigeminal nerve (see below), and also visual loss due to cytomegalovirus retinitis.

Defects of healing, skin lesions and ulcers

Very few HIV-infected persons have unblemished skin, and inspection in a good light often shows subtle signs suggesting the diagnosis. In a Lusaka dermatology clinic Hira and colleagues found that 98 per cent of 113 patients with AIDS and 54 per cent of 1009 with AIDS-related complex had one or more cutaneous lesions[14]. In addition, HIV-infected patients are predisposed to suffer severe drug reactions, particularly in response to antituberculous therapy.

In Zambia the incidence of herpes zoster has increased 20-fold since 1985 in young adults; 93 per cent of such individuals are seropositive for HIV antibodies. They suffer severe multidermatomal disease leading to marked scarring, which is a diagnostically useful incidental finding in many patients attending clinics for other reasons. The ophthalmic division of the fifth nerve is commonly affected, so commonly that colleagues in an eye clinic in Lusaka have started a prospective study of the effects of systemic acyclovir in the prevention of corneal scarring, iritis and secondary glaucoma, which often lead to blindness. Jellis, also in Lusaka, has seen painful osteoporosis following herpes zoster occurring on limbs, a condition which resembles Sudeck's atrophy[13].

Dryness and scaling, variable pigmentation, darkening of facial skin, folliculitis, seborrhoeic dermatitis, molluscum contagiosum, and extensive tinea versicolor are other non-specific but suggestive signs of HIV infection. Many patients develop an itchy rash early in the course of infection and this recurs at intervals. In the acute stage there are tiny macules or papules (which ooze a little fluid when scratched); they are most numerous on the chest, both back and front. Small but permanent and characteristic scars result; they have a centre lighter than normal skin, which is outlined by a fine line of deeper pigmentation. When more than two or three scars are seen HIV infection is almost certainly present Histolology of the acute lesions shows a lymphoplasmacytic angiitis[14].

Some surgeons find that wounds heal slowly or break down in HIV-infected patients, while others maintain that if sepsis is controlled and a normal haemoglobin level achieved, healing takes no longer than usual, and in particular, that split skin grafts take readily. However, skin ulcers may develop on the extremities for which no arterial, venous, metabolic, neuropathic or factitious cause can be established. This is an area where prospective studies are needed by surgeons of different specialties working in different geographical locations.

Urologists in Lusaka are seeing an increase in the incidence of urethral strictures with perineal fistulae in HIV-infected patients. These fistulae are slow to heal after suprapubic urinary diversion, but once closed, the underlying stricture can be treated successfully by endoscopic urethrotomy, as in any other patient

Several urologists have seen unexpected wound breakdown after operations to repair vesicovaginal or rectovaginal fistulae in HIV-infected women and one urologist in Tanzania has started a prospective study of this difficult problem.

Specific genital ulcers, particularly those due to herpes simplex type 2 and to *Haemophilus ducreyi*, are larger and more aggressive than usual in HIV-infected patients, and they are slow to heal and quick to recur. Genital warts are a well-known manifestation of HIV infection everywhere, but both patient and surgeon question the diagnosis and search desperately for effective treatment when they are extensive, aggressive and resistant to excision, even after diversion of the faecal stream by colostomy.

Tumours and tumour-like conditions

Disseminated Kaposi's sarcoma is part of the original case definition of AIDS, but its association with HIV infection cannot be explained in terms of breakdown in immune surveillance alone (why don't common tumours such as carcinoma of the lung or colon increase in incidence?), and several clinicians and pathologists no longer regard Kaposi's sarcoma as a true tumour[15,16].

HIV-related Kaposi's disease in Africa has several manifestations which may require surgical care, even if this is limited to biopsy. The commonest symptom is weight loss (76 per cent), but the most frequent specific sign is symmetrical lymphadenopathy (71 per cent), often accompanied by dark red or purple plaques on the hard palate or gums (58 per cent), with or without irregular hyperpigmented plaques on the skin of the trunk, face or limbs (40 per cent). In contrast to African endemic Kaposi's disease, where nodules occur on the distal parts of limbs, African atypical Kaposi's disease is centripetal in distribution, and oedema, when it occurs, is also often central. Plaques on the face are surprisingly symmetrical, and so is pulmonary infiltration, which is present at diagnosis in 42 per cent of patients and very common in the terminal stages of the illness. It is sometimes accompanied by rapidly recurring bloody pleural or pericardial effusions[16]. Of all patients with African atypical Kaposi's disease seen in Lusaka 95 per cent are seropositive for HIV.

In Lusaka we have seen two adults with acute intussusception due to multiple Kaposi's lesions in the small bowel, but as endoscopic experience shows that over half of all patients with African atypical Kaposi's disease have multiple gastrointestinal lesions we wonder why this particular surgical complication is so infrequent[17].

Thrombocytopenia may complicate HIV disease, but when it occurs with African atypical Kaposi's disease a 2·0 mg dose of intravenous vincristine often stops bleeding, restores a normal platelet count and initiates regression of the skin lesions.

In my opinion treatment of African atypical Kaposi's disease with cytotoxic drugs is always worthwhile, as objective regression occurs in 60 per cent of patients, and rapid relief of symptoms improves the quality of life. Life-table curves show median survival durations of over 3 years in patients with favourable signs, although those with pulmonary infiltration, central oedema, or weight loss in excess of 10 kg often develop recurrent disease after 3–4 months, and their median survival is only 7·5 months[18].

Nasopharyngeal carcinoma has not been as common in Zambia as it has been in Kenya, but in recent years we have seen more cases in younger patients, and several positive tests for HIV antibodies suggest non-coincidental association. We intend to investigate this possibility prospectively.

Carcinoma of the cervix is more likely to be causally associated with HIV infection. The incidence is rising and advanced tumours are presenting in younger women. Moreover, these carcinomas behave aggressively, often leading to death in less than a year from diagnosis. Several studies in the West have shown a marked increase in the incidence of cervical dysplasia in HIV-infected women, so that our observations are not unexpected although they need verification by formal studies

Burkitt's lymphoma is another virus-associated tumour which may be expected to show a change in incidence or behaviour, as already noted on the west coast of America. In Lusaka we have not seen a change in childhood disease yet, but we have seen two cases in HIV-positive adults who presented with abdominal masses. One died before treatment could start, but the other had a complete response to chemotherapy with marked improvement in his health.

Changes in tumour behaviour in HIV-infected patients are difficult to evaluate because the range in behaviour of human malignancies is so wide. However, anecdotal experiences suggest that common tumours, such as carcinoma of the breast, or (in our circumstances) hepatocellular carcinoma, behave more aggressively in HIV-infected patients than they do in others of comparable youth. Well-controlled prospective studies are needed, using several centres in one region, to address this question. Meanwhile management decisions may be taxing, as in the case of a woman who presented at the age of 25 with systemic recurrence of a carcinoma of the breast treated by mastectomy a few months earlier. She was HIV-positive and 2 months pregnant, with a family of young children.

New pathologies

Among the florid presentations of familiar diseases and the unexpected complications of standard operations we are observing some pathological processes which seem to be genuinely new.

Non-specific cystitis. One urologist is investigating inflammation of the urinary bladder in HIV-positive men, which leads to persistent microscopic haematuria and has a characteristic appearance at cystoscopy, but which is not associated with recognized bladder pathogens (B. Elem, personal communication).

Chronic osteitis. Jellis and Cairns in Zambia[13] have seen several young adults with fairly advanced HIV-disease who presented with pain in bones which appeared normal on examination, except for local tenderness. Symptoms often involved two or more sites, for example femur and tibia or both upper tibiae. (This motif of symmetry is common in HIV-related pathology.) The inflammatory process usually spread across joints, and multiple sinuses developed with progressive joint contractures. Radiographs showed patchy rarefaction apparently originating in the medullary cavity, but no reactive new bone and often no distinct sequestrum. Staphylococci were cultured from some (but not all) sites at surgical exploration, and a vigorous search in one case found no fungi. Curretted granulations showed no special histological features. If bacterial sensitivities were known and the correct antibiotic was given for a long period the osteitis might improve slowly, but the following case report shows that this was not always so. A man of 35 presented with a non-specific symmetrical osteitis of both upper tibiae and both lower femora in May 1987. Multiple sinuses developed but no sequestra of any size appeared. The knees contracted and severe pain was difficult to control. Biopsies showed non-specific inflammation, fungi were not found, and no consistent bacterial isolation was achieved. There was little response to penicillin or to a variety of other antibiotics, all given in high dosage. The patient requested amputation and his right leg was amputated through the upper thigh in January 1988. Efforts to save the other leg were maintained until August 1988 when the patient demanded its removal for pain relief. Since then he has gained weight and both stumps remain healthy and pain-free.

Vascular disease. Peripheral vascular disease is uncommon in African patients, even the elderly, and reconstructive surgery for femoral insufficiency or aortic aneurysm is very rarely required. However, we have seen a few young HIV-infected patients who presented with peripheral gangrene implying occlusion of medium sized arteries in the leg, which progressed proximally, requiring high amputations.

Recently we have seen vascular insufficiency of both legs in a 28-year-old woman who had an anaphylactoid reaction to self-prescribed ampicillin taken for painful swelling of one leg Both legs were swollen and cool, with normal sensation, but neither femoral nor distal pulses could be felt in either limb.

In one leg several patches of full-thickness skin loss occurred, and in this limb pulses have not yet returned, although 6 weeks after the acute episode pulses are palpable in the other foot. She is moderately wasted, and has scars of maculopapular dermatosis on her skin and antibodies to HIV in her blood. We have no explanation to offer for the reversibility of arterial obstruction in this patient. A man, with similar signs, was seen during the same week, but he died shortly after admission, and before testing for HIV antibodies could be undertaken.

Non-traumatic aneurysms are very rare in Zambia, so the following case was unusual. A man of 40 had African atypical Kaposi's disease diagnosed by lymph node biopsy in 1984, and responded well to cytotoxic drugs. Antibodies to HIV were demonstrated when he was first tested in 1986. In January 1989 he returned to the clinic complaining of pain in the left side of his neck, and repeated chest infections. I did not find any signs of cutaneous or oral Kaposi's disease but lymphadenopathy persisted. There was a systolic bruit over a pulsatile swelling in his left supraclavicular fossa, and I made a clinical diagnosis of an aneurysm, suspecting that it was mycotic. He was investigated for this but no sign of infection was found and an arch angiogram showed two fusiform aneurysms of the arch of the aorta, and small saccula aneurysms in the brachiocephalic and left subclavian arteries. Right hilar adenopathy with segmental collapse was an incidental finding. This man returned to the clinic in August 1989, still in reasonable health, with no increase in the size of his aortic aneurysms on plain radiography, and no active Kaposi's disease. The only new finding was multiple tender spots in the skin of his left hand, suggesting infected emboli from the subclavian aneurysm, so that we have started long-term antibiotic administration.

Does HIV infection influence the outcome of surgical treatment?

At present this is a difficult question to answer. Most surgeons can tell stories of sick patients who made an uneventful recovery from major surgery for desperate pathology, much to the surprise of all observers. Equally, most surgeons have seen patients in whom HIV-related pathology was not suspected at admission, but who suffered a rapid and progressive decline in health following necessary surgery, and did not leave hospital alive.

Watters and colleagues in Lusaka tested 396 admissions to the intensive care unit at the University Teaching Hospital for antibodies to HIV during a 12-month period during 1985 and 1986, finding 21 per cent to be positive[19]. They compared the outcome of admission to the intensive care unit in seropositive and seronegative patients with different diagnoses, and found no significant differences in hospital mortality for any diagnosis except pneumonia Differences in mortality rates were seen but failed to reach significance for severe gynaecological sepsis[7]. They concluded that HIV infection alone should not exclude patients from the benefits of ICU care, although those who were severely ill with directly HIV-related pathology rarely survived, an experience which matches that of others in the West[20].

Blood transfusion

The human immunodeficiency virus is a permanent reminder that only autologous blood is safe, as blood from any other person may carry yet-to-be-discovered pathogens. Risks of transmitting HIV by transfusion of blood or its products can be reduced to acceptably low levels in low incidence areas, but not always in populations where seroprevalences of 10 per cent or more are found and all sexually mature adults are in a 'risk group' This means that blood may be drawn from recently infected persons who are viraemic, but who have not yet produced antibodies to titres detectable by standard screening kits. Moreover, new and established donors are afraid to offer blood as they know testing will be done. Consequently a long-standing shortage of blood for transfusion has become acute in some of our cities.

We advocate the following seven basic strategies to minimize risk:

1. Reduce the need for transfusion by efficient care for pregnant women, children with sickle cell anaemia, and those at risk for malaria
2. Use autologous blood for all planned major surgical operations and, where possible, for emergency operations
3. Select donors to avoid persons with high-risk behaviour
4. Test donated blood for HIV antibodies using specific and sensitive tests which have been validated against panels of local sera
5. Prepare all clotting factors by prolonged heat treatment
6. Seek sensitive and specific tests for HIV antigens which are cheap enough to allow large scale use in blood banks
7. Recruit 'low risk' donors for emergency supplies from unorthodox age groups such as young adolescents and the elderly.

Eshelman and colleagues in Tanzania have reduced their use of homologous blood from over 51 per cent of patients having open prostatectomy to only 4 per cent, by a policy of taking one unit of blood from patients 5–7 days before surgery. They have shown that this is safe at any age providing that the patient is passed as fit for general anaesthesia and has a haemoglobin level of 9·3 g/dl or higher. They give oral haematinics during the week prior to surgery[21].

Conclusion

One hundred years ago a few inquisitive and energetic men were tramping around Africa, meeting a variety of people and exploring the astonishing mountains, lakes, and rivers in their paths. Our explorations may yield less attractive discoveries, but we should accept that we too are explorers of new territory, and take the trouble to record our findings with the diligence and enthusiasm of our predecessors

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I am deeply in debt to many colleagues who have shared their experiences with me, and allowed me to mention the early findings of studies which are far from complete. I am particularly grateful to John Jellis, James Cairns and David Watters, from whom I received many helpful comments during the preparation of this paper. Finally, I am grateful to the AIDS Surveillance Committee for permission to present this work.

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Announcement

The British Journal of Surgery Subscribers Questionnaire

In April of this year all subscribers to the Journal in Great Britain and Ireland were sent a questionnaire asking for their opinions on its content and for suggestions for possible improvements.

The response was much greater than anticipated and the editors would like to thank all those who took the trouble to reply. However, because of this large response, we were unable to comply with the wishes of some respondents in their choice of book from our list. To these people we apologise, and hope that the alternative book supplied proves useful.

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Surgical management of anorectal disease in HIV-positive homosexuals

One thousand and ninety human immunodeficiency virus (HIV)-positive homosexual or bisexual males were seen in one hospital for management of HIV disease over a 9-year period. One hundred and fifty-five patients were referred by acquired immunodeficiency syndrome (AIDS) physicians for general surgical management. The most frequent reason for surgical referral (64 patients) was anorectal disease which occurred in 5·9 per cent of all HIV-positive patients. One or more diagnoses were reached in 61 of the 64 patients referred with anorectal disease: warts (38 per cent of diagnoses), anorectal ulceration (26 per cent), perianal sepsis (15 per cent), neoplasia (14 per cent) and haemorrhoidal disease (8 per cent). Anorectal symptoms were relieved in 68 per cent of patients and the median survival of those treated was 17·5 months from the time of surgical referral. Both warts and perianal sepsis were associated with in situ *neoplasia, but no case of progression from* in situ *to invasive anal squamous carcinoma was detected. The aetiology of anorectal ulcers was not clear, but surgical excision of anal ulcers and skin tags can produce healing. Palliation of anorectal symptoms in HIV-positive homosexual patients is possible but some conditions are unusual and surgeons should be familiar with their presentation and management.*

Keywords: HIV disease, anorectal disease, surgery

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By the end of 1988 a total of 4375 male homosexuals in the UK were known to be infected with the human immunodeficiency virus (HIV)[1]. Within the next 5 years up to 20000 homosexuals in the UK will be similarly infected[2]. To date, with the exception of a few inner city hospitals, HIV disease has had little impact on UK general surgical workload However, as HIV-positive patients increase, surgeons will increasingly be asked to treat HIV-associated conditions.

Initial experience of surgery in HIV-positive patients was predominantly of diagnostic lymph node biopsy, but clinical familiarity with HIV disease soon reduced the need for this[3]. Anorectal disease is now the most frequent reason for surgical referral of HIV-positive patients in this hospital. To evaluate the novel management problems created by anorectal disease in HIV-positive patients, we have examined the prevalence, pattern and results of surgical treatment of anorectal disease in a population of HIV-positive homosexual or bisexual males seen up to the end of 1988.

Patients and methods

All HIV-positive homosexual or bisexual male patients attending one inner city hospital before 1 January 1989 were included. These patients were primarily managed by acquired immunodeficiency syndrome (AIDS) physicians unless a surgically remediable complication was suspected Thus patients with anorectal conditions such as infective proctitis[4] and neuropathic faecal incontinence[5] were not referred for surgical opinion. The study included only those patients with anorectal symptoms who were referred for surgical consultation – usually including examination of the anal canal and rectum under anaesthetic – and, where appropriate, for treatment. Details of symptoms, diagnosis, management and outcome were recorded for all patients. The stage of HIV disease was classified as· HIV-positive, Centers for Disease Control (CDC) group 2, HIV-symptomatic, CDC groups 3 and 4a, and AIDS, CDC group 4b–4e[6]

Results

One thousand and ninety HIV-positive homosexual or bisexual male patients were seen between 1980 and 1989. Median follow-up was 18 months. One hundred and fifty-five patients were referred for surgical opinion during the course of their follow-up of whom 64 (5·9 per cent of all HIV-positive homosexual patients) required management of anorectal symptoms. Six patients were referred on more than one occasion. Using contingency table analysis, the proportion of patients in each HIV disease category was not significantly different for patients with anorectal symptoms (HIV-positive 32 per cent, HIV-symptomatic 43 per cent, AIDS 25 per cent) compared with the overall HIV-positive population (HIV-positive 43 per cent, HIV-symptomatic 42 per cent, AIDS 15 per cent).

Diagnosis

A diagnosis was made in 61 patients but not in the remaining three patients. In five patients two diagnoses, e.g. warts and squamous carcinoma, were made. The diagnosis could be classified into one of five broad groups: anal and perianal warts (38 per cent of diagnoses), anorectal ulceration (26 per cent), perianal sepsis (15 per cent), neoplasia (14 per cent) and haemorrhoidal disease (8 per cent).

Anal and perianal warts. All but one (who refused treatment) of the 25 patients with warts were treated either by diathermy or excision. Eight patients had no residual warts 1 month after excision, seven patients required further treatments, and ten patients failed to attend for follow-up review. Neoplasia was identified in three of the 16 patients from whom excised wart-bearing tissue was sent for histological examination (squamous carcinoma *in situ* in two and Kaposi's sarcoma in one patient). One of the patients with carcinoma *in situ* died of AIDS 18 months after local excision without local recurrence, while the other remains recurrence-free after 3 years The patient with an anal canal Kaposi's sarcoma associated with warts has developed generalized Kaposi's sarcoma lesions in the skin and gut, but there has been no local recurrence of the anal canal lesion 1 year after local excision.

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Anorectal ulceration. Six patients had rectal ulcers. Herpes simplex virus (HSV) was identified in three of these, while the ulcers were associated with distal proctitis in two cases, and solitary rectal ulcer in one patient. Two of the HSV-positive ulcers responded to acyclovir while the third rapidly subsided spontaneously. Ulcers in one of the HSV-negative patients with proctitis responded to metronidazole and erythromycin, but the second patient with proctitis, who was treated with cefuroxime and metronidazole, did not respond.

Two patients had ulcers in both anal canal and rectum. In both cases the rectal ulcers resolved with acyclovir treatment after a presumed diagnosis of HSV infection, but in both cases the anal ulcers persisted.

Eight patients, including those two with ulcers in both anal canal and rectum, had chronic anal ulcers. Although these ulcers were situated at the anal verge and were frequently adjacent to oedematous skin tags, they were more broad-based than fissure *in ano* and were not restricted to the midline. In five of these cases there was no evidence of HSV on culture or histology. No anal ulcer responded to acyclovir, even where HSV was identified. Seven of the eight patients were treated by ulcer and skin tag excision; four healed without complication, two healed after 1 month, and one patient died of AIDS before follow-up.

Three further patients with posterior midline fissure *in ano* have been included in the ulcer diagnostic group. Two of these fissures resolved after abstinence from anal sex and the third continued to bleed until it was excised. Histology showed non-specific inflammation with no evidence of HSV.

Perianal sepsis. Five patients with perianal abscess and two with submucous abscess situated low in the rectum[7] were treated by incision and drainage. Healing eventually occurred in all cases although in one a second drainage procedure was required within a month, and in another a fissure *in ano* developed which was excised 6 weeks after original drainage. Histological examination of abscess wall tissue removed from the five patients with perianal abscess revealed one Kaposi's sarcoma (which recurred locally before the patient died of AIDS) and one squamous carcinoma *in situ* (which had not recurred 6 weeks after operation).

Two patients presented with perianal sepsis associated with a low intersphincteric anal fistula. One healed within a month of laying-open and the other after further laying-open 4 weeks after the initial procedure. A further patient with a high intersphincteric fistula was not treated in view of previous reports of poor healing and faecal incontinence in HIV-positive patients[8].

Neoplasia. Nine (14 per cent) out of 64 patients with anorectal symptoms had a previously undiagnosed malignant anorectal neoplasm. Histology of excised anal warts revealed two squamous carcinomas *in situ* and one Kaposi's sarcoma (see *Warts* above). Histology of abscess wall removed at incision and drainage of perianal abscess revealed another squamous carcinoma *in situ* and another Kaposi's sarcoma (see *Perianal sepsis* above). Two further patients with symptoms and signs suggesting acute ischiorectal abscess were found to have non-Hodgkin's lymphoma invading the ischiorectal fossa and lower rectum when examined under anaesthesia. Transperineal biopsies were taken from both, and a rectal biopsy was also taken from one who subsequently developed a malignant fistula *in ano*. One further patient who presented with anal pain had a bulky squamous carcinoma which involved the rectum. He underwent abdominoperineal resection of rectum and had delayed wound healing and persistent perineal sepsis until his death from AIDS 13 months later. The final patient in this group had bleeding from a low rectal Kaposi's sarcoma.

Haemorrhoidal disease. Four patients with haemorroids and one with perianal haematoma were referred for control of symptoms All four with haemorrhoids were treated by phenol injection without complication and with resolution of symptoms within 1 month. Symptoms from the perianal haematoma resolved spontaneously

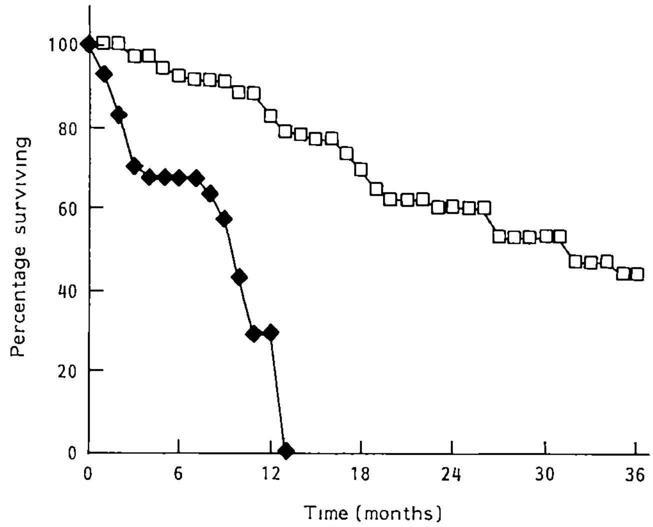

Figure 1 *Survival from time of treatment for anorectal symptoms in 12 patients with AIDS (—◆—) and 46 HIV-positive patients without AIDS (—□—). Mean survival in the former group was 8 months and in the latter group 27 months*

Outcome

Fifty-six patients underwent a surgical procedure after surgical referral for anorectal symptoms. Fifteen were lost to surgical out-patient follow-up after operation, 12 of whom were patients with warts who failed to attend the surgical out-patient clinic after excision. Twenty-eight (68 per cent) of the 41 patients seen at follow-up were symptom-free 1 month after surgery. Survival after surgical referral in 58 patients from time of surgical referral (median 17·5 months) is shown in *Figure 1*

Discussion

The incidence of anorectal disease requiring hospital admission in this study of homosexual and bisexual males was roughly 14 times greater than that of the general adult male population in England (Hospital In-Patient Enquiry; Office of Populations, Censuses and Surveys, unpublished tables). Previous reports have suggested that 15 per cent of male homosexuals with AIDS-related complex (ARC) or AIDS[8] but only 4 per cent of non-homosexual ARC and AIDS patients[9] undergo surgery for anorectal disease. In the present study, anorectal disease was not restricted to the most immunosuppressed patients. Although some of the conditions treated, e g. Kaposi's sarcoma, are associated with profound immunodeficiency, the distribution of stage of HIV disease in these patients with anorectal symptoms was not significantly different from that of the general HIV-positive homosexual and bisexual population. The large excess of anorectal disease in the HIV-positive population studied is best explained by the combination of homosexual behaviour[10–12] with immunodeficiency.

It has previously been suggested[8] that over 30 per cent of homosexuals with ARC and AIDS experience symptoms from anorectal disease at some stage during their illness, and that 50 per cent of those with anorectal symptoms undergo surgery. This is considerably more than the 5·9 per cent rate of surgical referral in the HIV-positive population studied here, and reflects the filtering of HIV-positive patients with anorectal symptoms by AIDS physicians before surgical referral. As a result of this filtering of non-surgical conditions such as infective colitis and virally-induced neuropathic incontinence, 85 per cent of patients referred for surgical opinion required surgery. The incidence of surgery among patients who have died of AIDS in the present study (13 per cent) is similar to that (15 per cent) previously reported[8].

The commonest anorectal condition treated was warts. The high incidence (19 per cent) of neoplasia in these warts suggests that histological examination of warts in HIV-positive patients should be routine. In the three cases where *in situ* squamous carcinoma was present, local excision achieved complete control over a median follow-up of 18 months. The 48 per cent of HIV-positive wart patients who did not attend for regular follow-up might be reduced if these patients were warned of the risk of malignant change. The incidence of invasive squamous carcinoma is increased in immunodeficiency[13–15], but the risk and interval of progression from *in situ* to invasive carcinoma is unknown. Moreover, one of the cases of *in situ* squamous carcinoma in the present series was not wart-associated, so patients with warts are not the only ones at risk. Many more asymptomatic HIV-positive patients may have had anal carcinoma *in situ* which could have been detected by anoscopy screening[16]. However, in this study of over 1000 HIV-positive homosexual patients over a median follow-up of 18 months, no case of progression from carcinoma *in situ* to invasive carcinoma was identified, and only one case of invasive squamous carcinoma occurred. The prognosis for untreated *in situ* carcinoma would have to be worse than that for HIV disease before surveillance programmes, involving both increased patient anxiety and resources, could be justified.

Symptoms from anorectal ulceration resolved in 88 per cent of cases within 3 months. The cause of these ulcers is not clear. HSV was isolated in 47 per cent and may have been present in others who were not specifically cultured for HSV. However, other pathogens including HIV may also be responsible. While most rectal ulcers responded to medical treatment – particularly acyclovir – anal ulceration was more resistant. However, surgical excision of anal ulcers was associated with symptom relief in 88 per cent of cases. Current policy for anal ulcers is to swab for HSV and examine stools for cryptosporidia. If present, HSV is treated with oral acyclovir (400–800 mg × 5/day) or, for resistant strains, with a 14–21-day course of intravenous foscanet. Surgical excision with histological examination for viral inclusions of cytomegalovirus or HSV is reserved for patients who are resistant to medical treatment.

Experience from other centres with large AIDS populations (S. Wexner, Symposium on Anal Sex, Section of Coloproctology, Royal Society of Medicine, London, February 1989, unpublished) has suggested that complex perianal sepsis is frequent. This was not our experience. In all but one case of perianal sepsis the septic focus could be drained without major perineal dissection. In the only patient with a high anal fistula in our series, laying open was not attempted because of previous reports of delayed healing in AIDS[8].

There was a high incidence of anorectal neoplasia (14 per cent) among HIV-positive patients with anorectal symptoms. Careful examination of the anal canal and rectum under anaesthetic with biopsy of suspicious lesions is mandatory. Care should be taken before 'incising and draining' suspected ischiorectal abscesses to establish that they are not solid tumours[17]. In view of the risk of fistula *in ano*, we now avoid transanal biopsy in favour of biopsy through the perineum or ischiorectal fossa.

Results from the small group of patients with haemorrhoidal disease suggest that HIV-positive homosexuals with symptoms of haemorrhoidal disease can be treated by phenol injection with similar results to those obtained in the general population.

Although the prognosis in HIV-positive patients is limited, the median survival of patients treated in this study was 17·5 months and symptoms were relieved in 68 per cent – results which compare favourably with palliative surgery for many neoplastic conditions. Careful examination and treatment is worthwhile and can help to reduce anorectal symptoms in patients with HIV disease.

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Colon wound management and prograde colonic lavage in large bowel trauma

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Between 1983 and 1987 prograde colonic lavage was prospectively evaluated in 389 patients with colon trauma. Predefined high risk patients had exteriorization of the primarily sutured colon. Intraperitoneal primary closure was otherwise used. Patients received prograde colonic lavage by random allocation. The healing exteriorized colon was interiorized 5–10 days after the initial surgery. The median age was 29 years and only 28 patients were women. Injuries were due to stab (316), gunshot (54), shotgun (10) or blunt trauma (9). Exteriorization of the primarily sutured colon was carried out in 217 patients of whom 101 had prograde colonic lavage. Twenty (9 per cent) died. Of the survivors, 150 (76 per cent) had their colon successfully interiorized and this rate was unaffected by prograde colonic lavage. Intraperitoneal primary closure was performed in 172 patients of whom 91 had prograde colonic lavage. Seven (4 per cent) died. Mortality was directly related to the number of associated injuries. Prograde colonic lavage, irrespective of the type of colonic wound management used, did not reduce the mortality rate, which was 7·2 per cent for those who had such lavage and 6·6 per cent for the rest. Prograde colonic lavage cannot therefore be recommended in colon trauma.

Keywords: Colon-traumatic, infection, wound

Colon injury is still widely recognized as one of the most serious intra-abdominal injuries in civilian practice because of the lethal consequences of peritoneal contamination[1,2]. The dramatic improvement in survival brought about by exteriorization of the injury as a colostomy during the 1939–45 war is well known and has led to strong support for its extensive use in civilian practice[3,4], in the belief that disruption of a suture line plays a major role in morbidity and mortality. However, most civilian injuries result from stab or low velocity gunshot wounds which cause less tissue destruction than high velocity injuries. In addition, reduction of the injury to operation time, aggressive resuscitation, and early administration of antibiotics have contributed to improved survival irrespective of how the colon wound is managed[5]. For these reasons the need for routine colostomy has been questioned.

Recognition of this is reflected in the growing support for intraperitoneal primary closure in certain conditions under which it has been found to be safe[6–10]. However, consistent with the concern for suture line failure and the belief that the injury should be isolated outside the peritoneal cavity, many surgeons have practised exteriorization of the primarily sutured colon with successful early replacement in as much as 75 per cent of patients. This avoids the morbidity and extra hospitalization for colostomy closure[9–11].

Previous reviews and continuous prospective audit of colon injury management at King Edward VIII Hospital, Durban have helped to establish policies for optimal treatment, and only intraperitoneal primary closure and exteriorization of the primarily sutured colon are routinely used in the management of the colon wound. Although selection of the type of colon wound management and overall patient care were considered to be satisfactory, the possibility that bacterial migration across the suture line had occurred was suggested by the death from septicaemia of four patients in a previous study[9]. These patients had relatively uncomplicated injuries; there was no faecal contamination at the initial operation, no evidence of colon wound disruption at autopsy, yet the peritoneal cavity appeared to be the focus from which the sepsis arose. In addition to the possibility of bacterial migration, the colonic flora provides a source of endotoxin, absorption of which may contribute to the severity of sepsis.

For these reasons intraoperative removal of all faeces from the colon should be beneficial and is feasible by the technique of prograde colonic lavage described by Dudley *et al.*[12]. The present prospective randomized study analyses the effect of colonic lavage in large bowel trauma.

Patients and methods

From 1983 to 1987 the clinical course of all patients admitted to King Edward VIII Hospital, Durban with colon injuries was monitored prospectively Data were recorded by the operating surgeon on a proforma sheet which was scrutinized daily by one of the authors and collated using a relational database program (dBASE III PLUS, Ashton-Tate, Torrance, California, USA) During the study colon wounds were managed routinely by one of two methods. Exteriorization of the primarily sutured colon was used when there was gross peritoneal soiling, delay from injury to operation of greater than 12 h, doubtful colon viability, or associated renal or diaphragmatic injury. Otherwise intraperitoneal primary closure was the technique of choice irrespective of the mechanism of colon injury Once the type of colon wound management had been decided the patients were randomized to have or not to have colonic lavage by the drawing of a sealed instruction. The study was approved by the ethics committee of the University of Natal Medical School and King Edward the VIII Hospital, Durban

Operative procedure

All patients had systemic broad spectrum antibiotic cover before induction of anaesthesia which was continued if overt peritonitis was present. Midline laparotomy was performed with the patients in the Lloyd-Davis position. The extent and priority of the injuries were assessed and the injuries dealt with appropriately. The colon wound edges were debrided and repaired in two layers, all coats continuous chromic cat gut followed by an interrupted seromuscular layer of braided polyester Colonic lavage, in those randomized to have it, was performed by a modification of the technique of Dudley *et al* (*Figure 1*)[12]. A 4 cm diameter corrugated anaesthetic tube was inserted into the rectum and kept in place with an anal purse string suture to

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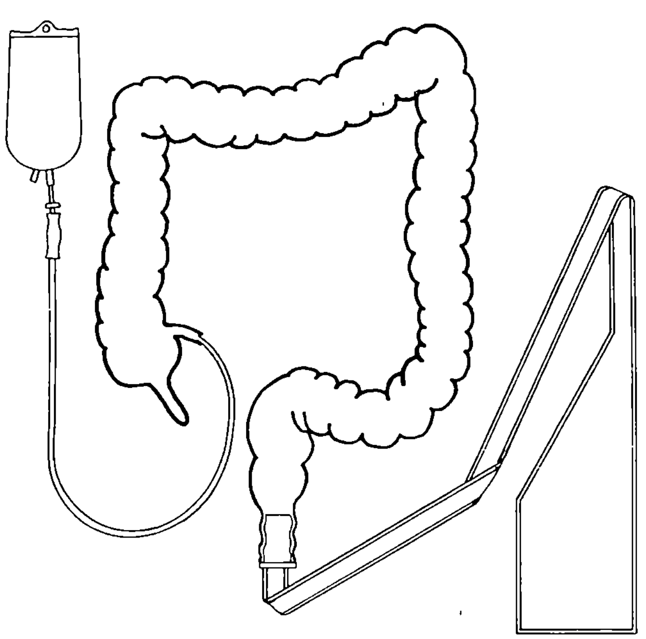


Figure 1 *Schematic representation of the technique of prograde colonic lavage*

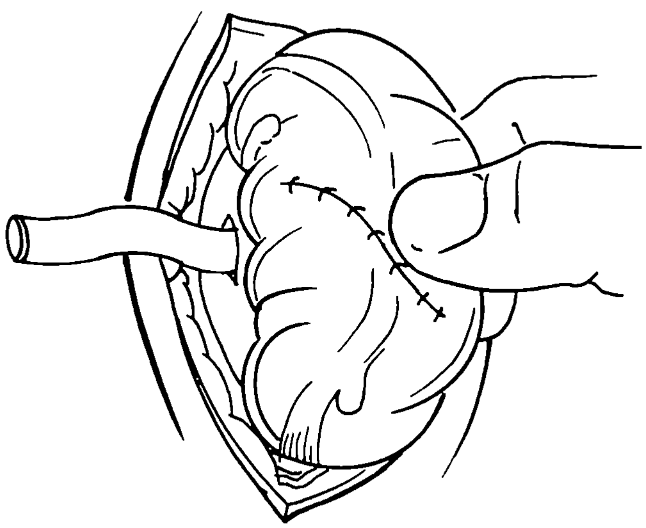


Figure 2 *Exteriorized primarily sutured colon*

allow collection of the faecal effluent. Before abdominal wound closure copious peritoneal lavage with warm saline was used to remove blood, intestinal content or pus from the abdominal cavity. A latex tube drain was placed adjacent to any intraperitoneal colon suture line and the subcutaneous wound was left open routinely

The technique of exteriorization has been previously described[9,11] and is shown schematically in *Figure 2*, but certain aspects require emphasis. A 10 cm abdominal incision must be made to allow free passage of luminal content distally and to prevent poor venous return and oedema of the colon wall Isolation in a transparent colostomy bag without dressings provides the best environment for healing[11] Providing the suture line was intact, the peritoneal cavity uninfected and intestinal activity had returned, the exteriorized loop was replaced in the peritoneal cavity under general anaesthesia using simple finger dissection This was usually between 5 and 10 days after the first operation. Dehiscence of the suture line resulted in a colostomy which was formally closed 6–15 weeks later

Statistical analysis was made using the Mann–Whitney U test to compare individual groups and the χ^2 test for differences in proportions between groups.

Results

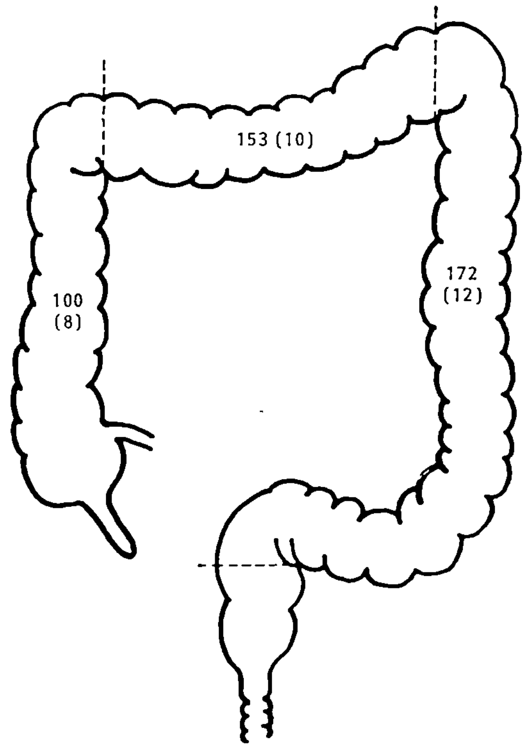
A total of 405 patients were entered into the study. Because of a breach of the management protocol 16 patients were withdrawn. The remaining 389 patients were analysed. The mean age was 29 (range 12–70) years and only 28 patients were women. The mechanism of injury and death rate by site is shown in *Figure 3*. The site of injury did not influence morbidity or mortality.

In 122 patients the colon was the only abdominal organ injured. The small bowel (145) was the commonest associated site of injury followed by the diaphragm (56), stomach (49) and liver (49). A total of 159 patients had one associated injury, 75 had two and 33 had three or more The mortality rate was 2·5 per cent for an isolated injury and 5 per cent for one, 13·3 per cent for two and 21 per cent for three or more associated injuries. Gunshot wounds had an average of 1·2 associated injuries whereas stab wounds had an average of 1·06. Those who had exteriorization had a total of 263 associated injuries compared with 137 in those who had intraperitoneal primary closure. The distribution and number of associated injuries was similar to those who had and those who did not have colonic lavage.

Exteriorization of the primarily sutured colon was carried out in 217 (56 per cent) patients and 101 of them had colonic lavage. Intraperitoneal primary closure was performed in 172 (44 per cent) patients of whom 91 had colonic lavage. The mortality and septic morbidity is detailed in *Table 1* and is reported for each type of wound management.

Exteriorized primarily sutured colon

The average delay between injury and operation in these 217 patients was 17·5 h. Of the 20 deaths in this group, ten occurred within 48 h of operation. In eight of these patients, intraperitoneal sepsis was the major contributing factor while



Patients (male, 361; female, 28)

Stab	316 (81 per cent)
Gunshot	54 (14 per cent)
Blunt	9
Shotgun	10
Total	389

Figure 3 *Mechanism and distribution of colon injuries (425 injuries in 389 patients). Numbers on diagram show number and site of injuries (number of deaths in parentheses)*

Table 1 *Mortality and sepsis from large bowel trauma related to colon lavage and type of colon wound management*

Patients	IPC ($n=172$) Lavage ($n=91$)	IPC ($n=172$) No lavage ($n=81$)	EPSC ($n=217$) Lavage ($n=101$)	EPSC ($n=217$) No lavage ($n=116$)
Deaths	5(4*)	2(1*)	9(7*)	11(10*)
Percentage	5	2	9	9
Sepsis				
Wound	20	13	17	19
Intraperitoneal abscess	4	2	3	0
Average hospital stay in days	16	16	24	25

IPC, intraperitoneal closure, EPSC, exteriorized primarily sutured colon; *sepsis related

two died of the effects of massive associated injuries rather than of complications related to colon injury or its surgical treatment. Of the ten patients who died between 3 and 34 days after operation, intraperitoneal sepsis was responsible in nine. The remaining patient with multiple injuries died on the third day after operation of the effects of prolonged hypotension. Sepsis was therefore responsible for 17 of the 20 deaths. The exteriorized colonic wound was found to be intact at autopsy in eight and there was no information in two.

Laparotomy wound sepsis occurred in 36 (17 per cent) patients. Five intraperitoneal abscesses occurred in three patients all of whom had colonic lavage. This complication did not occur in those patients who did not have colonic lavage.

The outcome of exteriorization is shown in *Figure 4*. The exteriorized colon was returned to the peritoneal cavity after an average of 7 days. Dehiscence of the exteriorized suture line occurred in 47 survivors, 24 per cent of the total, and their average hospital stay was 50 days. Early interiorization was possible in 76 per cent, 72 per cent for those who had colon lavage and 80 per cent for those who did not ($P>0{\cdot}05$). Those patients who had a successful interiorization and who had colonic lavage had a reduction of 3 days in their hospital stay compared with those who did not ($P=0{\cdot}006$) (*Figure 4*). In four patients clinically missed perforations were identified by colon lavage. Colonic lavage did not affect the mortality rate. Five patients developed a faecal fistula after return of the exteriorized colon to the peritoneal cavity. In three patients the fistula closed spontaneously. One fistula required re-exploration and exteriorization and the resulting colostomy was subsequently closed. The final fistula was in a patient who died from systemic complications. Gross disruption of the suture line after its return to the abdomen occurred in only one patient. He required repeated surgical debridement for abdominal wall necrosis following crush trauma and the wound broke down after 10 days. Despite segmental resection the patient died from abdominal wall sepsis. In five patients small bowel prolapse which required urgent surgical intervention occurred through the colon exteriorization wound. The small intestine and the sutured colon were returned to the peritoneal cavity without further morbidity.

The mortality rate for the 35 patients who had exteriorization for gunshot wounds was 23 per cent and for patients with stab wounds it was 6 per cent. Eighty one per cent of the survivors of gunshot wounds and 74 per cent of the survivors of stab wounds had successful early replacement of their colon.

Intraperitoneal primary closure

Average preoperative delay in the 172 patients in this group was 8 h. There were seven (4 per cent) deaths following intraperitoneal primary closure. Three patients died within 48 h of operation, one of multiple injuries and two of overwhelming septicaemia. Four died more than 48 h after surgery. One had brain death due to a head injury and life support was discontinued at 16 days. Three died of uncontrollable intraperitoneal sepsis. All of these patients had autopsies. None had colon dehiscence at autopsy through one patient had an unsuspected colonic disruption repaired at 7 days when his abdominal wound dehiscence was resutured. He eventually died of intraperitoneal sepsis but with a healed colon wound 138 days after the initial operation. Wound sepsis occurred in 33 of the 165 survivors in this group. Intraperitoneal abscess occurred in a total of six patients and two of these died Only two developed a localized abscess. The incidence of sepsis and mortality and the length of hospital stay were not significantly influenced by colonic lavage. The 19 patients with gunshot wounds treated by intraperitoneal primary closure survived, as did the four patients who had blunt injury treated by this method. The average period of hospitalization in the 165 survivors was 16 days irrespective of the mechanism of injury.

Sixteen patients who had intraperitoneal primary closure were withdrawn because the colon wound should have been managed by exteriorization due to delay in excess of 12 h (average 17 h). In 15 there was no peritoneal contamination and they all survived with an average hospital stay of 14 days. A 16th patient had intraperitoneal primary closure in the presence of severe peritonitis at 24 h after injury, a clear break in protocol, and he died from septicaemia within a further 24 h. The colon wound was intact at autopsy.

Colonic lavage irrespective of the type of wound management had no significant effect on the mortality rate which was 7·2 per cent for those who had colonic lavage and 6·6 per cent for those who did not.

Discussion

In the evolution of management strategies for large bowel injuries, colon suture line dehiscence has been regarded as a major risk factor in the development of postoperative complications.

Theoretically the production of collagenase by bowel organisms may weaken the collagen cross linkage which is necessary for suture line healing[13,14] and this might allow migration of organisms through the suture line and be a possible factor in the development of intraperitoneal sepsis. It follows therefore that a colon devoid of faeces may heal better and may reduce the incidence of septic complications. Strangand and Hagemann[15] have shown this experimentally and the efficacy of preoperative whole gut irrigation for elective colon resections has also been demonstrated by Hewitt *et al.*[16] The value of colonic lavage in emergency left colon resection for obstructing and perforated colon disease has been propounded by Radcliffe and Dudley[17] and Koruth *et al.*[18] They reported leakage rates of 6 per cent and 8 per cent respectively. More recently, however, the hallowed tradition of bowel preparation has been called into question by Irving and Scrimgeour[19] and Mealy *et al.*[20] In their studies all the faecal matter was not removed from the colon before resection and primary anastomosis, and they reported colonic dehiscence rates of zero and 7·2 per cent respectively Our findings tend to corroborate the results of Irving and Mealy's studies, because autopsy after death from

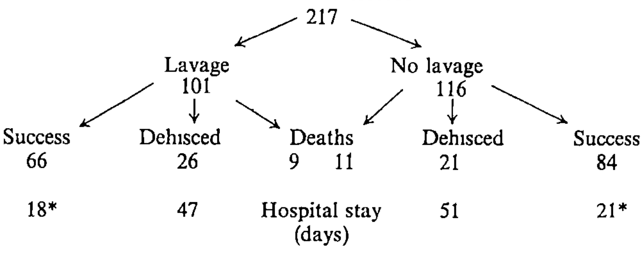


Figure 4 *Outcome of patients treated by exteriorization of the primarily sutured colon* *$P=0{\cdot}006$

intraperitoneal sepsis in those who had intraperitoneal primary closure revealed no leaks at the suture line whether or not colonic lavage had been performed.

Those patients, slightly over half the total, who were treated by exteriorization had a 24 per cent incidence of colon wound dehiscence. It is far from clear what caused this dehiscence but its frequency was not influenced by colonic lavage. Various reasons have been advanced such as concomitant sepsis elsewhere and intestinal obstruction, which was a cause in this study. The exteriorized sutured colon wound almost always breaks down in the presence of abdominal wound dehiscence, which suggests a common deficiency in wound healing. Technical factors, probably related to the frequency with which exteriorization was used, may explain the difference in results of various reported series. Dawes *et al.*[21] reported a 31 per cent incidence of intra-abdominal abscesses and only five of 16 patients had early return of bowel to the peritoneal cavity following this procedure. Demetriades *et al.*[22] failed to disclose the fate of the only three patients treated by this method in their series of 134 individuals. Others confirm its successful use with results similar to our own[9,23–25]. We believe the major reason for failure in those who use this method infrequently is that they make the exteriorization wound too small. Making the wound the correct size, however, does carry a risk of small bowel herniation but if this is promptly dealt with as in this series little harm results.

A trend to increased morbidity rate from both wound and intra-abdominal abscess was observed in those who had colonic lavage. This apparently deleterious effect of colonic lavage was offset in those patients who had a successful early replacement of their colon, in whom there was a significant reduction in hospital stay of 3 days. In addition, colonic lavage may have played a major role in reducing complications in the four patients in whom it identified unsuspected colon injuries. The evidence from this series confirms our previous experience[9] and that of others[7,23–25] that exteriorization of the primarily sutured colon is a preferable procedure to colostomy when exteriorization of the wound is considered to be necessary. This is because the high rate of successful interiorization saves these patients from a prolonged hospital stay and a second operation for colostomy closure. A procedure that has its own morbidity rate[9,11].

If gross colon wound dehiscence is not a significant source of mortality, what does determine outcome in patients with colon injuries? Mortality was directly related to the number of associated injuries in this study, which confirms Burch's data[25] and refutes the findings of some previous studies[8,9].

The major problem, however, in the management of colon trauma is the prevention and control of sepsis. In the present series 22 of the total of 27 deaths resulted from infection. The longer the interval between injury and operation the greater is the overall risk of developing postoperative sepsis[5,8]. The long preoperative delay (average 13·7 h) in the present study reflects referral patterns and a large volume of trauma admissions.

A long delay in the absence of peritoneal contamination can occur without ill effect and indicates that the bowel injury has been walled off. This is shown by the survival of 15 patients with sealed injuries who had excessive delay and who were withdrawn from this study because they had erroneously had interperitoneal primary closure instead of exteriorization, and by 12 similar patients in a previous study[9]. Their survival suggests that time on its own is not a determinant of prognosis. Delay plus gross faecal soiling, 'contamination time', may be a meaningful criterion on which to base management decisions. This is supported by the presence of faecal contamination and the higher incidence of sepsis in the exteriorized closure group, most of whom had a significant contamination at the time of surgery. However, some patients treated well within 12 h of injury died within 48 h of surgery from septic complications and, conversely, many patients first treated well beyond this time interval failed to develop postoperative sepsis.

Contamination and delay are significant factors but how should they be meaningfully integrated into management decisions? Stratification of the patients according to severity of injury is relevant and adoption of a selective policy of colon wound management has been used by us and others[9,26]. However, this is only a start, because the influence of injury on physiology is only partly considered. It would seem logical that APACHE II[27] or a similar comprehensive scoring system[28] should be adopted. This would allow more objective decisions to be made on how to manage the patient, and particularly to determine whether the type of colon wound management is important in the final outcome.

It should be appreciated that the opinions expressed here are based on a large experience of stab wounds as opposed to low velocity gunshot wounds. Although the mortality rate is higher in the latter, because of the increased number of associated injuries, there is little evidence to suggest that management of the colon wound produced by these two mechanisms of injury should be any different. That all those surviving gunshots who had intraperitoneal primary closure made an unremarkable recovery and that a successful early interiorization rate of 80 per cent was achieved in those who had exteriorized bowel supports this opinion.

In the final analysis, although colon lavage is theoretically appealing, it has not reduced the incidence of localized septic complications, nor has it altered the pathophysiological effects of existing peritoneal contamination. Hence, morbidity and mortality rates from colon trauma are not influenced by colonic lavage and its use in this setting cannot be recommended. The best results will be achieved in those patients in whom the effects of peritoneal contamination are reduced to a minimum by rapid admission to hospital, early administration of antibiotics and prompt surgical repair of the injuries, irrespective of the precise type of colon wound management. Indeed, it is our opinion that the contraindications to intraperitoneal primary closure, which is safe in selected patients[9,11,22,25,29], should be better defined, so that fewer patients are exposed to the morbidity rate of colonic exteriorization, particularly as a colostomy.

Acknowledgements

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Portable anorectal manometry

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In certain cases, the operative approach to anorectal disease may be dictated by anal sphincter function. It has recently been stated that assessment of sphincter function must often be based upon digital assessment rather than manometric studies because of the inaccessibility of the latter[1]. In order to circumvent the problem of accessibility to manometric investigations, we have developed an accurate, portable and inexpensive device which is useful for the assessment of sphincter function in an ambulatory setting.

Patients and methods

The hand-held anal manometer device is composed of an air-filled microballoon (Dipped Latex Products, Gloucestershire, UK), 10 mm long and 5 mm in diameter, similar to that described by Miller *et al.*[2]. The balloon is connected to the transducer port of a Stryker 295-1 intracompartmental pressure monitor (Stryker Corporation, Kalamazoo, Michigan, USA) (*Figure 1*) by capillary tubing with an internal diameter of 0·7 mm and an outside diameter of 2 mm. The balloon is slightly deflated when used to prevent any increase in pressure due to warming and expansion of air within the balloon. Pressures are recorded from the transducer with a Primeline SS-100F ® (Soltek, San Fernando, California, USA) series flatbed minirecorder. The total cost of the apparatus is less than £1000

Thirty-seven patients have been studied with this apparatus, nine males and 28 females (mean age 42 years, range 7–71 years). Nineteen patients had incontinence, six patients had full-thickness rectal prolapse, 11 had constipation, and one had encopresis. Patients were studied in the left lateral position after administration of a cleansing enema. To assess the accuracy of the system, a comparison was made with standard water perfusion manometry. This consisted of a Narco MMS ® (Narco Biosystems, Houston, Texas, USA) 100 system using a four-channel Arndorfer (Arndorfer Inc., Greendale, Wisconsin, USA) catheter with an outside diameter of 4·8 mm, previously described in detail[3].

A station pull-through was performed with each manometric system. Pressures were recorded at 1 cm intervals starting at 6 cm from the anal verge. Since pressures were recorded in four quadrants with the perfusion system, a simple average of the four values was compared

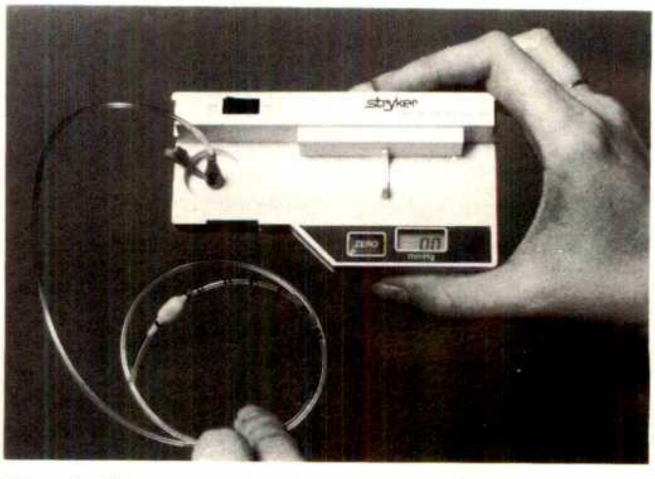

Figure 1 *The manometric equipment consists of a small, hand-held transducer/amplifier unit and an air-filled microballoon catheter. Pressures may be recorded directly from the liquid quartz readout or, alternatively, the output signal may be recorded on any compatible flatbed recorder*

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with values obtained from the air-filled portable system. Measurements were recorded at rest and during a squeeze effort. The sphincter length was assessed by the length of the resting high pressure zone[4]. The maximum resting pressure and the maximum squeeze pressure were recorded for each patient by both systems.

Results

The median sphincter length, maximum resting pressure and maximum squeeze pressure were 3·0 cm (range 0–4·0 cm), 44 mmHg (range 10–93 mmHg) and 75 mmHg (range 18–181 mmHg) for the air-filled system and 3·0 cm (range 0–4·0 cm), 41 mmHg (range 12–94 mmHg) and 85 mmHg (range 22–217 mmHg) for the water perfusion system. Maximum resting pressure, maximum squeeze pressure and sphincter length showed excellent correlation, with Spearman ranked correlation coefficients of 0·91, 0·91 and 0·89 respectively (*Figure 2*).

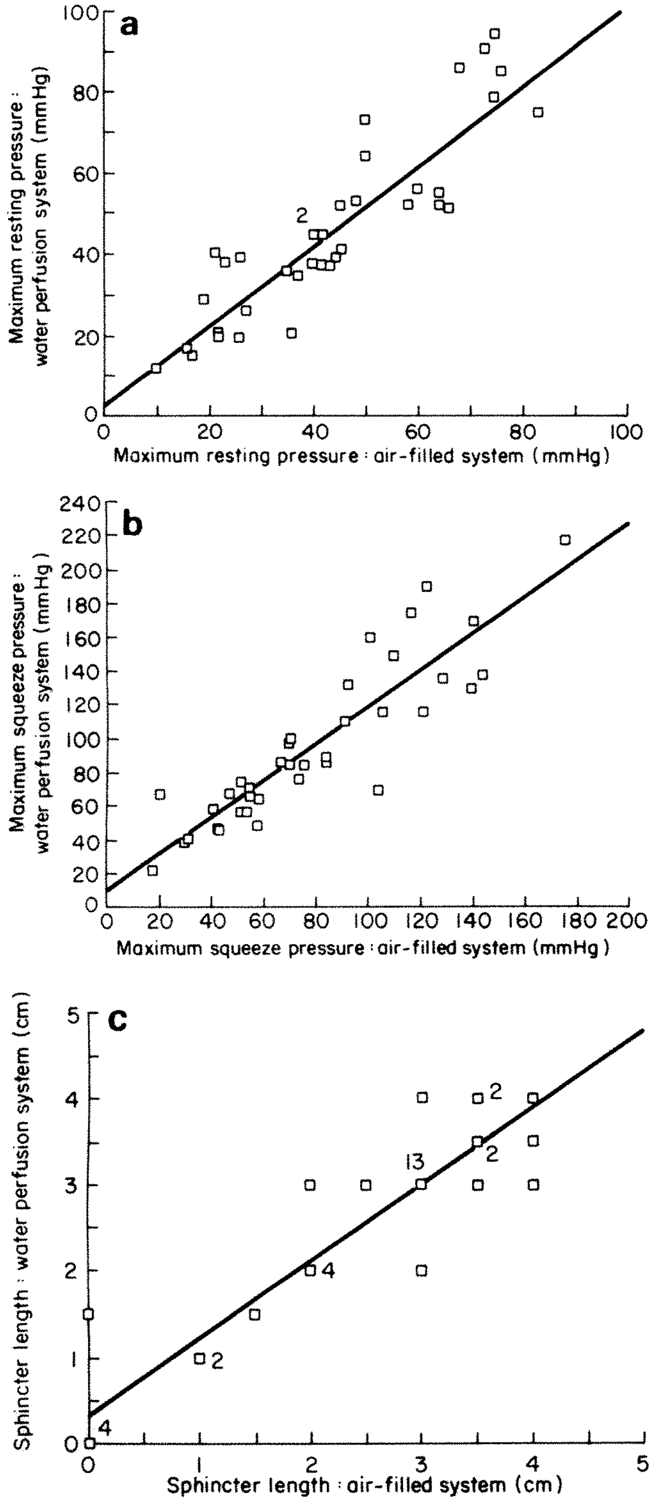

Figure 2 *Spearman ranked correlations for* **a** *maximum resting pressure* (r = *0·91*), **b** *maximum squeeze pressure* (r = *0·91*) *and* **c** *sphincter length* (r = *0·89*) *for each system. Regression lines are shown for each correlation. Numbers on plots indicate identical measurements in different patients*

Discussion

A recent study has shown digital estimation to be as accurate as anal manometry in the assessment of anal sphincter function[1]. However, this was based upon digital assessment performed by an experienced anorectal physiologist. Previous work in this area has shown digital assessment of sphincter function to be clearly inadequate[5]. The problem of accessibility has been addressed by this small, accurate and inexpensive system. We have found the system to be useful in clinical practice, correlating closely to anal pressure measurements obtained from our standard equipment. Each examination takes only 5–10 min to perform, enabling manometry to be performed in the out-patient clinic or at the patient's bedside. While it will not supplant the anorectal physiology laboratory, it will allow manometric evaluation of the anal sphincters to become more routine in the diagnosis and treatment of anorectal disorders.

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Mutagenicity of bile and duodenal adenomas in familial adenomatous polyposis

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Duodenal adenomas occur almost inevitably in patients with familial adenomatous polyposis (FAP) whereas gastric adenomas are rare. FAP patients are also at high risk of duodenal cancer. Within the duodenum, adenomas cluster around the ampulla of Vater, as do the majority of duodenal cancers, suggesting that bile plays a role in tumour development. We therefore tested duodenal bile from 29 postcolectomy FAP patients (27 of whom had duodenal adenomas) and 24 non-FAP patients for mutagenicity, using techniques that detect point mutations in bacteria. Results which appeared to show that FAP bile was more mutagenic than control bile could be accounted for by a feeding effect, elimination of which also eliminated 'mutagenicity'. Under the conditions of our assays we conclude that if bile is an important factor in genesis of duodenal tumours, it does not act by inducing point mutation.

Keywords: Polyposis syndrome, familial, bile, colorectal cancer, duodenal neoplasms

The distribution of adenomas and cancers in the upper gastrointestinal tract of patients with familial adenomatous polyposis (FAP) parallels mucosal exposure to bile. In an endoscopic study of 102 FAP patients, gastric adenomas were found in 6 per cent and duodenal adenomas in 92 per cent. There was pronounced sparing of the duodenal bulb relative to the periampullary region (adenomas in 9 per cent and 74 per cent respectively)[1]. Non-adenomatous gastric polyps, found in 45 per cent of patients, were present in the proximal stomach, which is usually free of bile, whereas gastric adenomas occurred in the distal stomach which may be subject to bile reflux[2]. Jagelman *et al.*[3] found duodenal cancers in 39 of 1255 FAP patients, 36 of these cancers being periampullary in position. There are at least two explanations for these findings. Firstly, bile from FAP patients may differ from normal bile, perhaps containing carcinogens produced by abnormal hepatic metabolism[4–6]. Secondly, FAP bile is not different from normal bile, but the gastrointestinal tract of FAP patients is abnormally sensitive to the tumour-promoting activity of bile acids[7]. We have tested the first possibility, namely that FAP bile contains carcinogens, by looking for mutagenic activity in duodenal bile from FAP patients and from non-FAP controls.

Patients and methods

Control patients

An appropriate postcolectomy control group was not available for the following reasons: (1) colectomy is performed for sporadic colorectal cancer, but we wished to use in the control group patients demonstrably not at high risk for intestinal neoplasia: (2) postcolectomy patients with ulcerative colitis are, like FAP patients, at high risk of colonic dysplasia, carcinoma and hepatobiliary cancers[8,9]; (3) colectomy is sometimes performed for constipation, but the number of patients is small and gastroscopy is not usually indicated. Thus, having regard to the strictures placed upon us by the Ethical Committee, we were only able to use non-colectomy patients in whom gastroscopy was clinically indicated. Accordingly 24 (mean age 49·3 years, range 22–81 years, 13 men, 11 women) non-polyposis patients undergoing clinically indicated upper gastrointestinal endoscopy were recruited into the study (Ethical Committee Approval Numbers 88/4/10, 88/5/12).

FAP patients

Duodenal bile was collected from 29 FAP patients (mean age 42·1 years, range 26–65 years, 20 men, 9 women). All patients had undergone colectomy (24 had colectomy and ileorectal anastomosis, five had proctocolectomy and ileostomy, of which four were continent or pouch ileostomies and one was conventional). Duodenal adenomas were present in 27 of these patients, including a microadenoma in apparently normal mucosa in one patient. One patient without duodenal adenomas had mucosal hyperplasia on random duodenal biopsy, leaving just one other with an apparently normal duodenum.

Ideally, precolectomy FAP bile would have allowed a comparison between like groups, but gastroscopy is rarely performed before colectomy in FAP patients. Similarly, to obtain more precise matching, consideration was given to using bile aspirated from the gallbladder at the time of colectomy. However, this bile was at risk of contamination with a mutagenic antibacterial drug (metronidazole[10]) given before operation to all colectomy patients at St. Mark's Hospital.

Bile collection

Bile was aspirated via an endoscopically placed duodenal tube. A bolus intravenous injection of cholecystokinin (1 Ivy unit/kg) or ceruletide (5 μg) was given to augment bile flow. Bile samples were cooled, their pH was measured and the samples were stored at −70°C.

All patients consumed normal 'Western' diets. Nine of 24 controls and 11 of 29 FAP patients were smokers.

Mutagenicity assays of bile

In preliminary experiments, untreated bile samples were tested for bacterial mutagenicity using a standard agar-overlay method[11,12]. Since bile is a product of hepatic metabolism we did not supplement the mutagenicity assays with a rat liver postmitochondrial supernatant, which is the usual source of mammalian metabolic activation in the Ames test[11].

Assays were performed in triplicate using 50, 100 and 200 μl of bile per plate with *Salmonella typhimurium* TA98 and TA100 and *Escherichia coli* WP2*uvrA*pKM101. These assays showed that the base-pair substitution mutant *S. typhimurium* TA100 was the strain most sensitive to what appeared to be mutagenic activity in a proportion of bile samples. Further assays were then performed using this strain, with and without 1000 units per plate of *E. coli* β-glucuronidase (Sigma Chemical Company, Poole, UK) to deconjugate putative mutagens present as glucuronides. Bile from 23 FAP patients and 21 controls was tested in this way. To check that the dose-related increases in revertant colonies seen in several of the bile samples were ascribable to mutation rather than to increases in 'plate mutants' caused by feeding of auxotrophic (*his*−) bacteria by bile constituents[13], several of the most active samples were assayed at 200 μl per plate in the absence of the low level of histidine normally added as part of the assay[11,12]. These experiments showed that feeding rather than mutation was the most likely explanation of the positive results obtained with some of the bile samples. To avoid this artifact, bile samples from 18 FAP patients and nine controls were retested in a more sensitive assay in which 10^9 bacteria are incubated with the test substance in a total volume of 0·2 ml for 90 min before mixing with 2 ml of molten soft agar supplemented with histidine and biotin and plating on minimal agar (Kado assay)[14]. We modified the assay by washing the bacteria

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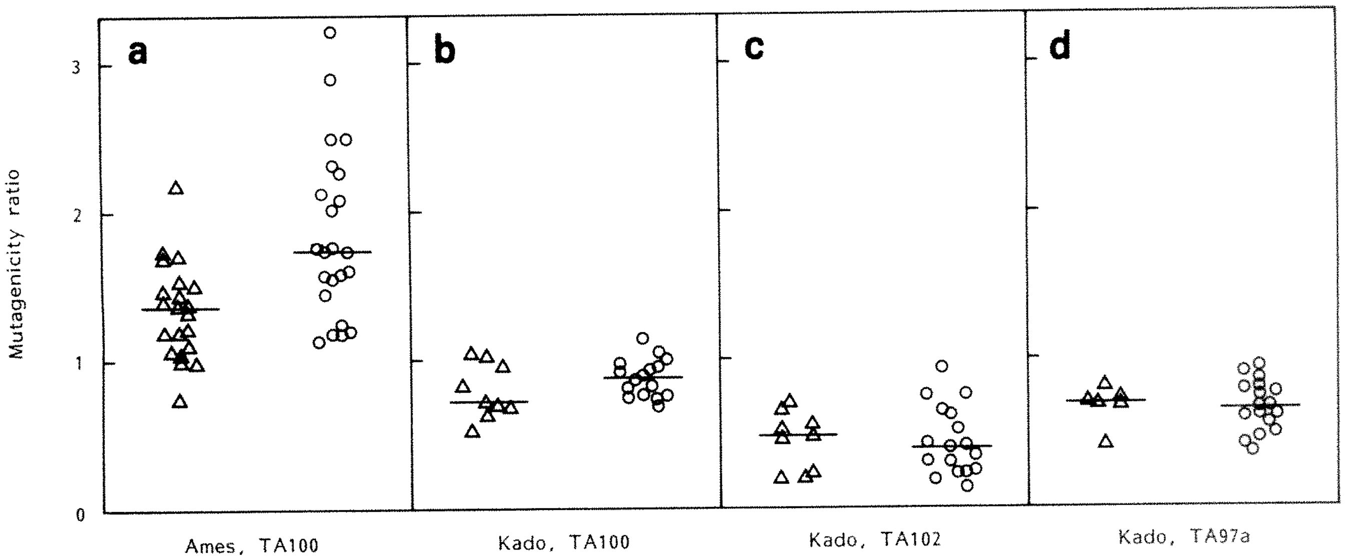

Figure 1 *Mutagenicity ratios of bile samples tested at 200 μl per plate from control patients and familial adenomatous polyposis (FAP) patients. The vertical scale represents the mutagenicity ratio defined as: mean* his+ *revertants on bile-treated plates/mean* his+ *revertants on untreated plates. The horizontal bar (—) represents the median mutagenicity ratio for each group of patients. 'Ames' refers to standard Ames test protocol; 'Kado' refers to Kado protocol modified by washing bacteria after treatment and before plating out. TA100, TA102 and TA97a refer to respective* his− *strains of* S. typhimurium. △, *control bile;* ○, *FAP bile. Ames test;* $P<0·001$

twice in 1 ml of ice cold phosphate-buffered saline to remove bile before addition of the top agar and plating out. As well as *S. typhimurium* TA100, these assays employed *S. typhimurium* TA97a and TA102. TA97a is particularly sensitive to the mutagenicity of frameshift mutagens, while TA102 is more eclectic than TA100 in its response to a variety of mutagens[11].

In addition to testing untreated bile, where sufficient material was available, we tested concentrated bile extracts prepared from samples which appeared to be mutagenic in the preliminary assays. Bile extracts were treated with XAD-4 resin by the method of White and Schwartz[15]. A volume of 2 ml of washed resin was placed in a 100 × 4 mm glass chromatography tube. Then 5 ml of bile was passed through the resin, followed by 10 ml deionized water. The resin was then eluted with 10 ml acetone. The eluate was evaporated to dryness in a freeze dryer, and the residue taken up in 1 ml of dimethyl sulphoxide (DMSO). Aliquots (20, 100 and 200 μl) of the DMSO samples were tested in triplicate in *S. typhimurium* TA102 using the modified Kado method described above.

Medications given to patients at endoscopy (heparinized saline, ceruletide, pethidine, midazolam, Buscopan (Boehringer Ingelheim, Bracknell, UK), cholecystokinin) were assayed for mutagenicity by the standard method[11] and gave negative results.

Reference mutagens (cisplatin, 4-nitroquinoline-N-oxide (4NQO)) were used as positive controls.

Results

Effect of bile on performance of the standard assay

All bile samples tested were pH > 7, consistent with the absence of gastric contamination.

Addition of 200 μl bile per assay did not affect the mutagenicity of 4NQO tested in *S. typhimurium* TA100 at doses of 0·05, 0·1 and 0·2 μg per plate. The assay without bile gave a slope of 6·1(0·49) mean(s.d.) revertants per ng, compared with 6·28(0·47) with bile ($P>0·75$).

Tests of bile using standard assay

There was no significant difference between assays conducted in the presence or absence of β-glucuronidase. The data were therefore pooled and are summarized in *Figure 1a* as mutagenicity ratios, obtained by dividing the mean number of revertant colonies per plate at 200 μl of bile by the mean zero dose value. The median mutagenicity ratio for controls was 1·36, compared with 1·73 for FAP patients ($P<0·001$, Mann–Whitney *U* test). Bile from one of 21 controls and nine of 23 FAP patients ($P=0·007$, Fisher's exact test) gave positive results as judged by a doubling or more of the background mutation accompanied by a statistically significant dose response. Of the 23 FAP patients whose bile was tested by this method, 19 had undergone colectomy and ileorectal anastomosis (of whom seven were positive) and four had a proctocolectomy and ileal pouch (two positives). Neither smoking (controls 1 of 1, FAP 2 of 8) nor the severity of duodenal polyposis were related to bile samples with mutagenicity ratios equal to or greater than two.

Table 1 *Parallel assays of 200 μl bile with and without standard level of histidine in the top agar*

Sample	+ Histidine	− Histidine	Bacterial lawn in absence of histidine
Control	121	0	No
LG23	159	123	Yes
FC27	125	119	Yes
JA25	171	136	Yes
FS24	150	93	Yes
MT12	117	85	Yes
EK3	99	40	Yes
Positive control 1 μg cisplatin	494	0	No

Values are mean colonies per plate

The largest increase in mutant colonies was a trebling of the background, much of which could have been caused by an increase in plate mutants generated by bacterial feeding[13]. To check this possibility, some of those bile samples which were 'positive' were tested at 200 μg per plate in the absence of the low level of histidine normally added to the top-agar to allow growth of auxotrophic bacteria[11]. The results are shown in *Table 1*. As expected, untreated bacteria did not grow in the absence of histidine. However, all cultures that received bile but no histidine developed confluent bacterial lawns and substantial numbers of revertant colonies. This was clear evidence that the positive results obtained could be explained by generation of spontaneous plate mutants resulting from increased growth of histidine-requiring bacteria, supported by nutrients present in bile, rather than by mutagenicity of bile constituents.

Increased sensitivity of modified Kado assay and effect of bile

Before retesting samples with the modified Kado method, we confirmed that this method was more sensitive than the

Table 2 *Mean mutagenicity ratios* obtained from modified Kado assays of control bile and familial adenomatous polyposis (FAP) bile*

Strain	Volume of bile per plate (μl)	Control patients		FAP patients	
		n	Mutagenicity ratio†	*n*	Mutagenicity ratio†
TA100	50	9	0·80(0·20)	18	0·82(0·11)
	100	9	0·78(0·22)	18	0·84(0·15)
	200	9	0·80(0·18)	18	0·86(0·12)
TA102	50	9	0·54(0·39)	18	0·36(0·18)
	100	9	0·49(0·32)	18	0·41(0·20)
	200	9	0·43(0·19)	18	0·42(0·22)
TA97a	50	6	1·04(0·16)	17	0·92(0·18)
	100	6	0·84(0·12)	17	0·87(0·17)
	200	6	0·66(0·13)	17	0·64(0·17)

* Mean number of revertant colonies on bile-treated plates/mean number of colonies on untreated plates; † mutagenicity ratios are presented as mean(s.d.)

standard Ames protocol, using 4NQO at doses of 0·01, 0·02, 0·05 and 0·1 μg per plate. The following slopes (mean(s.d.) number of revertants per ng) were obtained: Ames protocol, 5·6(0·23); Kado protocol, 15·2(1·7); modified Kado, 20·4(2·2), giving a 3·6-fold increase in sensitivity. Assays of bile using the modified Kado method in the absence of histidine showed that the washing step eliminated the growth enhancing effects of bile as judged by the absence of a bacterial lawn, and the appearance of only a few pre-existing *his*+ revertants.

Tests of bile using modified Kado method

No evidence of mutagenicity was discernible in untreated bile samples from 18 FAP patients and nine controls in any of the three bacterial strains tested (*Figure 1b, c* and *d*). There were no significant differences in the average mutagenicity ratios between control bile and FAP bile at any of the doses tested (*Table 2*). Ratios less than one indicate toxicity; bile from both groups of patients was slightly toxic to strains TA100 and TA97a (mutagenicity ratios ranging from 1·04 to 0·64) and rather more toxic to TA102 (0·54 to 0·36).

Bile which had been treated with XAD-4 resin (seven FAP patients) or with β-glucuronidase, or both, were also negative. Extension of the incubation of bile from three FAP patients from 90 min to 3, 5 or 24 h failed to demonstrate mutagenic activity of untreated or XAD-4-treated bile.

Discussion

In patients with FAP the pylorus provides a barrier to the development of adenomas and cancers, which occur less frequently proximal to the pylorus, whereas non-adenomatous polyps are common in this area. Distally, duodenal adenomas and cancers are found most frequently in the periampullary region[1,3]. Perhaps there is a general disturbance of growth control in the gastrointestinal tract of patients with FAP, which is expressed by a tendency to form polyps. Further differentiation of polyps (adenomas or not) may depend on local factors such as the presence of bile. Reflux of duodenal contents would then be necessary for the development of gastric adenomas[2]. In the absence of bile, non-adenomatous polyps would predominate.

The animal model for colon cancer in which an exogenous carcinogen, 1,2-dimethylhydrazine (DMH) is injected into rats, closely resembles FAP, producing a multiplicity of tumours; small-bowel and large-bowel tumours, clustering of small-bowel tumours in the vicinity of the ampulla, inevitability of cancer once at risk, and liver, bile-duct and brain tumours[16]. In this model, DMH metabolites are excreted in bile[17] although they may also reach the colon via the bloodstream[18].

These clinical and experimental findings suggest that bile is involved in the development of tumours. Although bile acids have been shown to be co-mutagenic[19] and co-carcinogenic[7], mutagenicity has not been demonstrated in the standard Ames assay[19–21] and conflicting results have been reported using bacterial fluctuation tests[22,23].

As well as showing that untreated bile contains enough nutrients to render interpretation of borderline results problematical, use of the standard Ames test protocol in the present study showed that if biliary mutagens exist, they are either very weak or present at low levels, or both, since we could not reliably distinguish true mutagenic effects over and above the 'noise' created by high levels of bacterial nutrients in bile. That significantly more FAP patients than controls produced bile samples that enhanced bacterial growth indicates a difference in bile between the two groups which is not connected with mutagenicity but may reflect some other biliary attribute. The *his*G46 mutation in *S. typhimurium* TA100 – the strain with which these standard Ames tests were conducted – occurs in the first structural gene of the histidine operon and blocks the formation of phosphoribosyl-ATP from ATP and 5-phosphoribosyl-1-pyrophosphate (PRPP)[24]. This is ten steps before the production of histidine. Thus, any of the ten intermediates which follow PRPP in the biosynthetic chain could act as a substrate for histidine biosynthesis and, if present in bile, would support the growth of *his*– bacteria.

In order to increase sensitivity and eliminate artifacts caused by biliary nutrients we used the method of Kado *et al.*[14] with the addition of a washing step to remove the bile from the bacteria before plating them out. To increase the chances of detecting mutagenic activity we employed two sensitive strains, *S. typhimurium* TA102 and TA97a, in addition to TA100, which is itself very sensitive to the mutagenicity of a wide range of mutagens. Moreover, where there was sufficient material, bile samples were extracted and concentrated with XAD-4 resin, and in some cases, extended incubation times were employed, up to a maximum of 24 h. Eliminating feeding by the washing step eliminated 'mutagenicity'; thus despite manoeuvres aimed at increasing sensitivity, we did not detect mutagenic activity in any of the bile samples tested.

The FAP bile examined in this study came from postcolectomy patients. It could be argued that colectomy may have diminished the putative mutagenicity of FAP bile, in view of the proposal that colonic bacteria may play an important role in intestinal carcinogenesis[25]. However, duodenal adenomas and cancers grow despite removal of the colon. This is borne out by evidence from the upper gastrointestinal surveillance programme at St. Mark's Hospital. Included in this programme are three patients (two of whom provided bile for this study) each with an identical history of colectomy and ileorectal anastomosis, excision of rectal stump cancer, duodenotomy and duodenal clearance for large and histologically worrying polyps, followed by recurrence of severe duodenal polyposis at an average of 6 years after duodenotomy. In a separate study[3] of 57 upper gastrointestinal cancers in 1255 patients, 50 occurred many years after colectomy.

If, by analogy with DMH-induced colon cancer in rats, FAP bile contains a carcinogen, our results indicate that this putative carcinogen is not a point mutagen, or that it is too weak or too dilute to detect with the assays used. Because bacterial mutagenicity tests do not detect genotoxic activity other than point mutation, we cannot exclude the possibility that bile might contain carcinogens which, though not point mutagens, cause chromosomal damage or aneuploidy, phenomena which have been implicated in colorectal carcinogenesis[26]. Alternatively, bile may act non-specifically by promoting the proliferation of cells which are already at high risk of malignant transformation[27], in which case any bile would do. Bile itself causes cellular proliferation[28,29], and has been shown to act as a tumour promoter in the DMH animal model[30].

We did find that duodenal bile from patients with polyposis had a greater capacity to support bacterial growth than bile obtained from controls. This may indicate an inherent difference between FAP bile and normal bile, or that colectomy caused this difference. Whatever the true explanation, this finding is peripheral to the central conclusion that none of the bile samples induced point mutations as judged by the assays we employed in this study.

Duodenal polyps in FAP patients are difficult to treat because of their sessile nature and periampullary position. The striking periampullary distribution of neoplasms suggests that manipulation of the bile of FAP patients might contribute to the resolution of this therapeutic dilemma. Such intervention could be dietary[31,32] or with agents such as calcium[33], antioxidants[34] or non-steroidal anti-inflammatory drugs[35], which may modulate the effect postulated of bile on the development of adenomas.

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Case report

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Endoscopic management of an unusual intrabiliary foreign body

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Endoscopic removal of gallstones from the biliary tree is an established procedure. Other obstructing agents that may be retrieved endoscopically include blocked stents previously inserted for palliation of malignant or benign biliary stricture and parasites such as *Ascaris lumbricoides* and *Clonorchis sinensis*[1,2]. We report the endoscopical removal of an unusual biliary foreign body, namely a broken limb of a T tube drain.

Case report

A 63-year-old man was admitted with a 5-day history of colicky abdominal pain in the right upper quadrant associated with fever and chills. Physical examination revealed tenderness with guarding over the right upper abdomen, and a provisional diagnosis of acute cholecystitis was made. Laboratory examination showed leukocytosis ($14{\cdot}4 \times 10^9$/l), hyperbilirubinaemia (39 μmol/l), and increased levels of alkaline phosphatase and alanine transaminase (199 units/l and 279 units/l, respectively). Oral cholecystography showed gallstones with non-visualization of the gallbladder. Ultrasound scan of the abdomen confirmed the presence of gallstones but the biliary system was not dilated. Endoscopic retrograde cholangiopancreatography (ERCP) showed a normal pancreatic duct but the common bile duct could not be cannulated. The patient underwent cholecystectomy and negative exploration of the common bile duct. A T tube was inserted for drainage and a T tube cholangiogram on day 8 showed free distal drainage. The T tube was removed on the ninth day but one of its limbs was missing and was presumed to have been left within the biliary system. An immediate cholangiogram through the T tube tract showed leakage of contrast into the peritoneal cavity but no filling of the common bile duct. To avoid a second laparotomy, ERCP was attempted with the purpose of removing the fragment endoscopically. Cannulation of the common duct again failed. A precut sphincterotomy with a needle knife resulted in active oozing from the sphincterotomy which required adrenaline injection for control. A third ERCP was deferred for 3 days to allow oedema to subside. This time cannulation was successful and showed a 2 cm tubular filling defect in the mid common bile duct (*Figure 1*). The sphincterotomy was extended and the T tube fragment was removed with a Dormia® basket (Olympus, Tokyo, Japan). Examination of the broken edge of the T tube suggested that a stitch had gone through the tube (*Figure 2*). An occlusion cholangiogram showed a slight irregularity at the mid common bile duct and a filling defect compatible with a stitch. No further attempt was made to remove the stitch because of its absorbable nature.

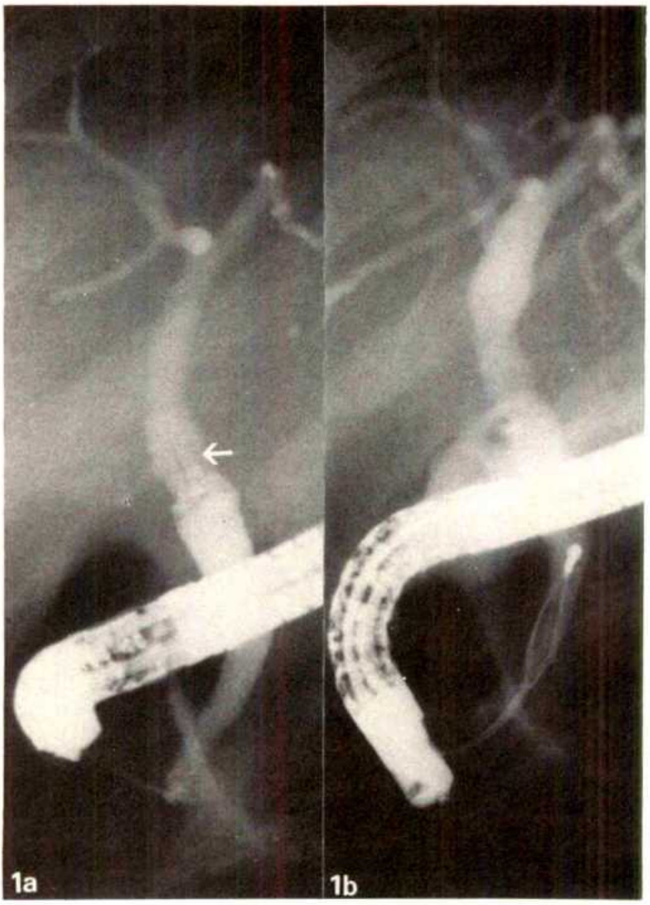

Figure 1 **a** *T tube fragment (arrowed) in the mid common bile duct; and* **b** *T tube fragment being retrieved by basket*

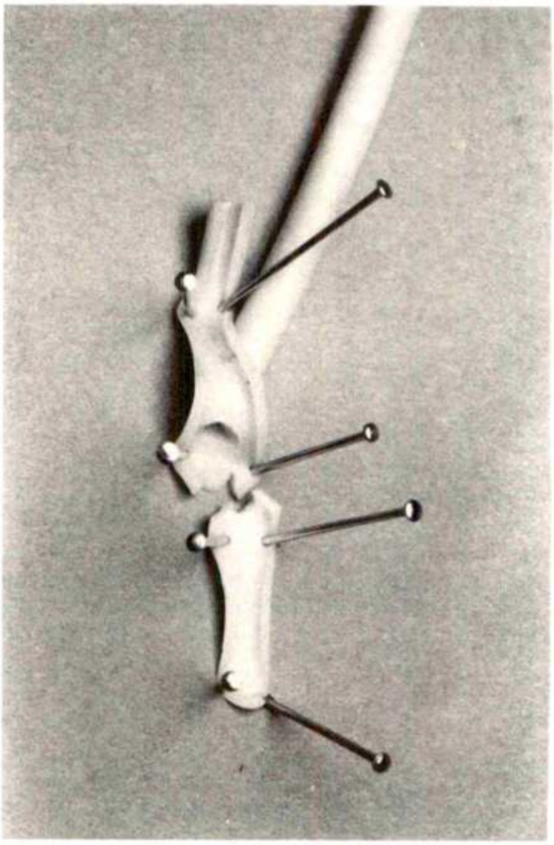

Figure 2 *T tube with the broken limb*

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Endorectal ultrasonography for the assessment of invasion of rectal tumours and lymph node involvement

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Sophisticated therapies for rectal carcinoma, such as sphincter preserving operations, pouch–anal anastomosis, preoperative irradiation or adjuvant chemotherapy, require an exact pretherapy assessment of the tumour and its lymph node involvement. A 7·0 MHz transducer was used before operation in the staging of 117 patients with rectal carcinoma or villous adenoma. In 90 per cent of cases it was possible correctly to stage the tumour before operation. Sensitivity for detection of perirectal fat infiltration was 97 per cent. Lymph node involvement was accurately identified in about 80 per cent of cases. Six carcinomas, which had developed within 31 examined tubulovillous adenomas, were detected by endorectal ultrasonography. No carcinoma remained undetected. Endorectal ultrasonography is a highly accurate tool for the staging of rectal carcinoma before operation and for the detection of lymph node involvement. Malignant change in tubulovillous adenomas are also detectable.

Keywords: Endorectal ultrasonography, preoperative staging, lymph node assessment

Sophisticated treatments for rectal carcinoma, such as sphincter preserving operations, preoperative irradiation or preoperative chemotherapy, require an exact pretherapy assessment of the tumour and its lymph node involvement. Endorectal ultrasonography is a diagnostic procedure which allows a direct and reproducible examination of the whole rectum[1–7]. During the examination the relationship of tumour to adjacent organs can be assessed and the presence of enlarged regional lymph nodes can be determined. So far, little has been done to determine the value of endorectal ultrasonography in the staging of small rectal carcinomas and its ability to discriminate between tubulovillous adenoma and carcinoma. The aims of the present study, therefore, were: (i) to determine the accuracy of endorectal ultrasonography in the staging of rectal carcinoma before operation with special regard to small carcinomas confined to the rectal wall; (ii) to establish criteria by which malignant change within tubulovillous adenomas might be detected; (iii) to evaluate sonographic assessment of lymph node metastases; and (iv) to describe the possible influences of sonography on the surgical treatment of rectal carcinoma.

Patients and methods

From January 1988 to August 1989, 117 patients were examined by endorectal ultrasonography. In 86 cases the indication for the examination was rectal carcinoma proven by rectoscopy and biopsy. In the other 31 patients sonography was used for the preoperative assessment of villous adenoma in order to detect malignant change within the lesion.

A 7·0 MHz radial scanner (Type 1846, Bruel and Kjaer, Denmark) was used. Focal length ranged between 2 and 5 cm. The total length of the rigid probe with the transducer fitted on top was 24 cm. The transducer rotated mechanically at a rate of 4–6 cycles per second, receiving the transmitted ultrasound at a 90° angle. Scanning radially to the rectal tube axis it provided a 360° display of the rectum and adjacent tissues. A thin rubber balloon was placed over the transducer and filled with 50 ml degassed water to provide an acoustic path.

The sonographic image

The use of a 7·0 MHz radial scanner always gives the same image of the intact rectal wall; five layers of echodensity can be discriminated – three echo-rich and two echo-poor layers (*Figure 1*). All three hyperechoic layers represent ultrasonic phenomena which are created when the ultrasonic beam enters and leaves an anatomical layer of a certain thickness[8]. The two hypoechoic layers represent the mucosa and muscularis propria of the rectal wall[3,6,9]. Identification of these two layers allows staging by the tumour node metastasis (TNM) system. The prefix 'u' has been added to signify a sonographic staging (uTNM). Based on the TNM system proposed by the Union Internationale Contra la Cancrum (UICC)[10] the tumours were defined as follows: uT$_1$, confined to the mucosa and submucosa (*Figure 2*); uT$_2$, confined to the rectal wall and leaving the third hyperechoic layer intact (*Figure 3*); uT$_3$, penetrating into the perirectal fat (*Figure 4*); and uT$_4$, penetrating into surrounding organs.

Inflammatory enlarged lymph nodes appear hyperechoic with

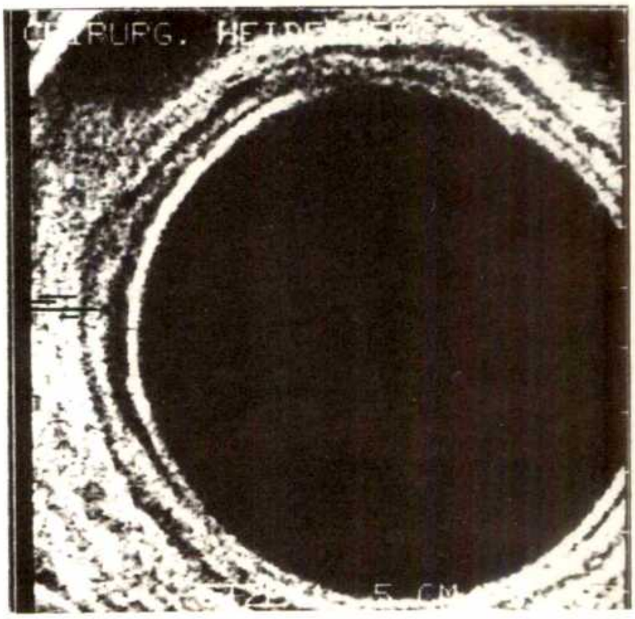

Figure 1 *Normal rectal wall with three hyperechoic and two hypoechoic layers*

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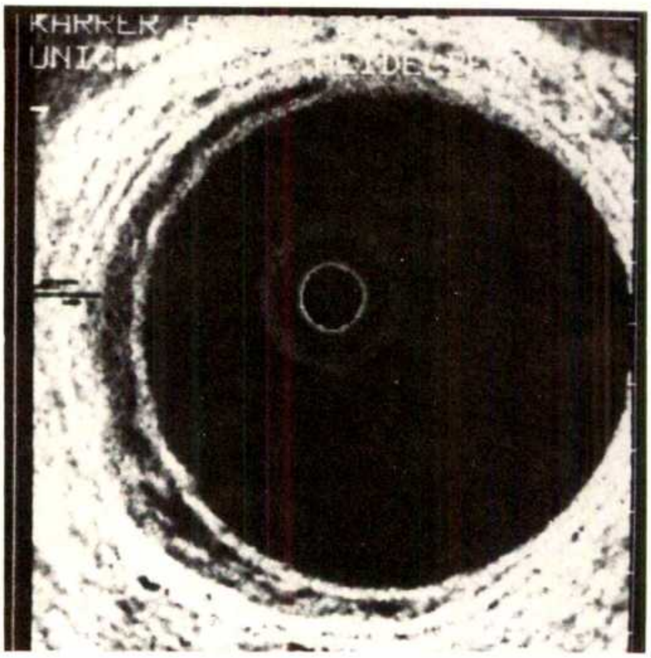

Figure 2 *uT$_1$ tumour, confined to the mucosa and submucosa, indicated by the broadening of the first hypoechoic layer on the right side of the rectal wall*

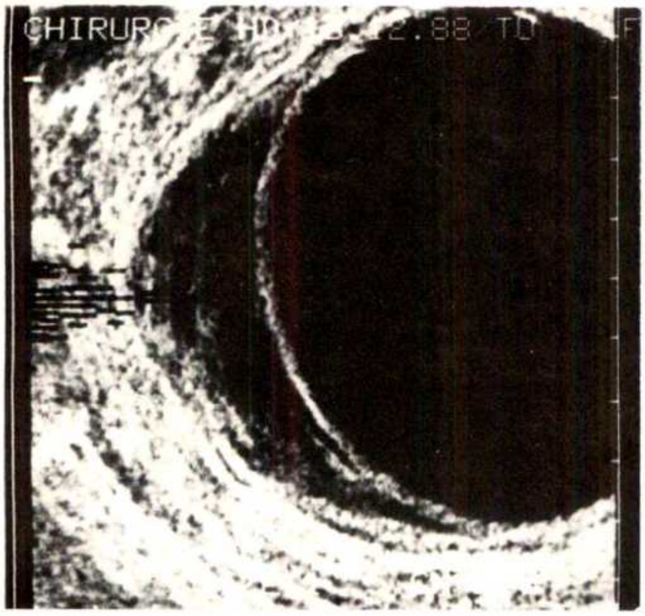

Figure 3 *uT$_2$ tumour: the second echo-rich layer is interrupted and the tumour reaches the muscularis propria*

indistinct margins in the surrounding tissue (*Figure 5*). In contrast, completely tumour-infiltrated lymph nodes resemble black holes with the same density as the tumour[1–13] (*Figure 6*).

Like a uT$_1$ carcinoma, the villous adenoma spreads within the mucosa of the rectal wall. This leads to a broadening of the first hypoechoic layer in both a uT$_1$ carcinoma and a villous adenoma (*Figure 7*). To distinguish these two tumours an assessment of echodensity is necessary. The villous adenoma usually appears as homogeneously echo-rich with strong reflections, whereas the uT$_1$ carcinoma is echo-poor. This makes it possible to discern malignant changes within a villous adenoma (*Figure 8*).

Results

Clinical staging

In 61 (71 per cent) of 86 patients with rectal carcinoma a complete clinical staging according to Mason[14] was possible. Fifteen tumours were unreachable by digital examination. A further ten tumours could be palpated only at their lower margin with the index finger. Twenty-four tumours were located in the lower third, 33 in the middle third, and 29 in the upper third of the rectum. Forty-seven (77 per cent) of 61 tumours were correctly staged by clinical examination (*Table 1*). Of 29 tumours clinically confined to the rectal wall (clinical stages I and II), five were understaged and three were overstaged. In three cases the tumour was thought to have penetrated the perirectal fat, but pathological examination showed only an infiltration of the muscularis propria. In two cases infiltration of adjacent organs was not detected by clinical examination.

Staging by endorectal ultrasonography

All 86 patients could be examined by endorectal ultrasonography. Ten additional tumours had to be excluded from this study

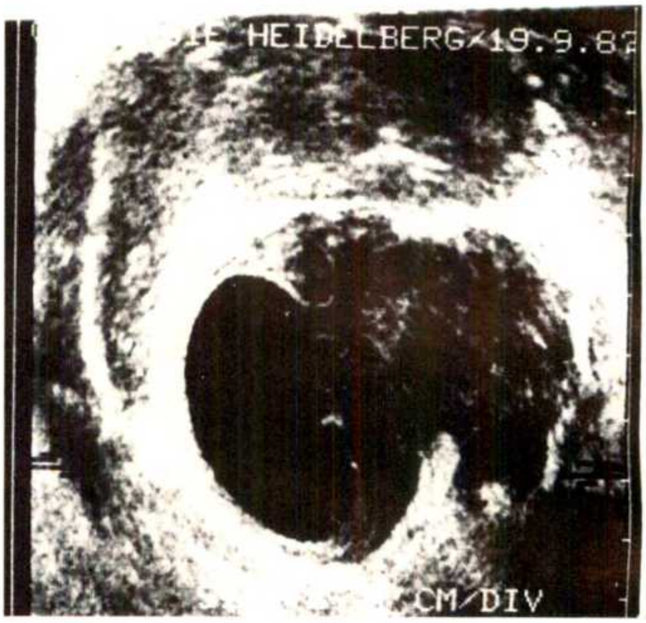

Figure 4 *uT$_3$ tumour penetrating into the perirectal fat*

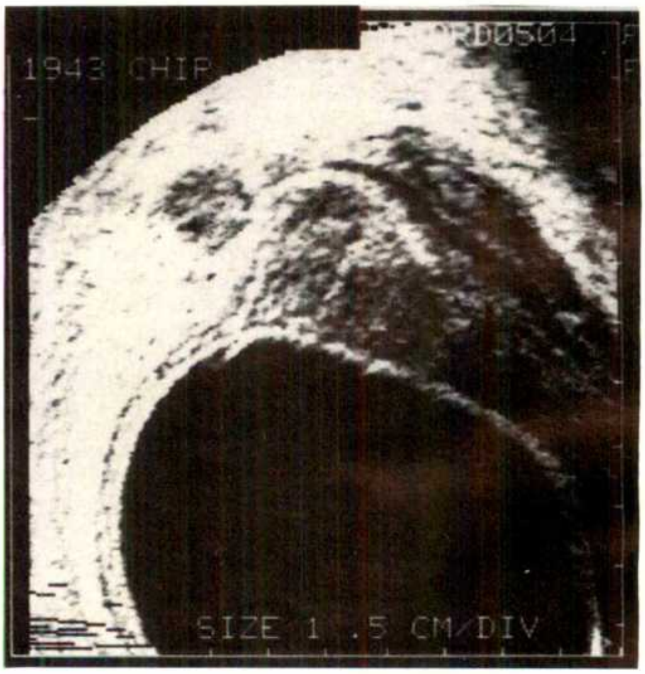

Figure 5 *Inflammatory enlarged hyperechoic lymph node in the 11 o'clock position*

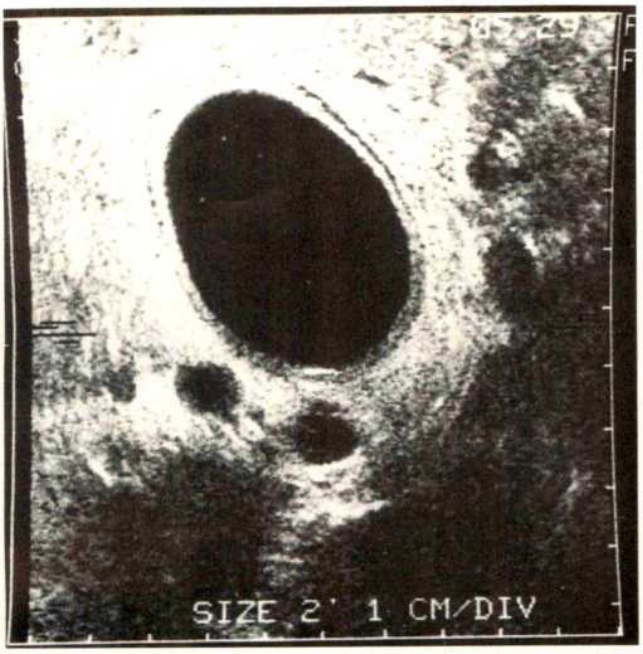

Figure 6 *Several tumour-infiltrated lymph nodes, showing as black holes, in the perirectal fat*

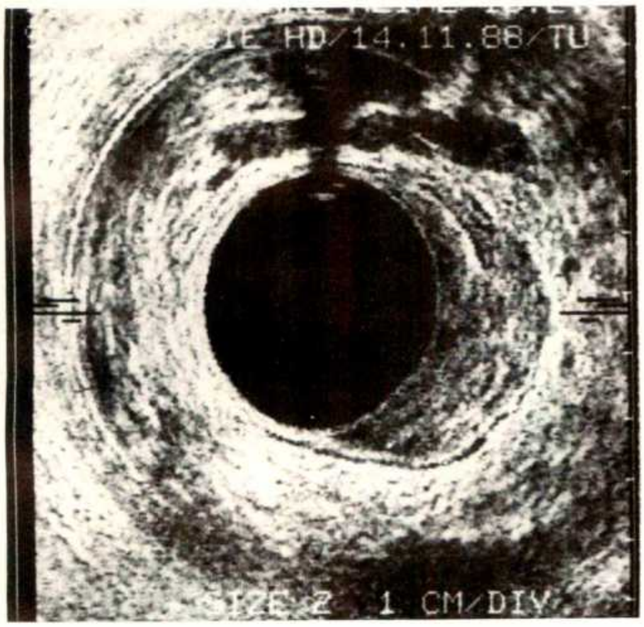

Figure 7 *Villous adenoma with its typical echo-rich pattern*

because stenosis of the rectum prevented passage of the instrument. Of the 14 tumours sonographically staged as uT_1, 12 were correctly staged and two were understaged when compared with pathological assessment (*Table 2*). Three tumours were overstaged in the uT_2 group and four in the uT_3 group. Eight tumours showed infiltration of adjacent organs and these were staged correctly despite stenosis of the rectum (which still allowed the instrument to pass).

Altogether 76 (88 per cent) of 86 sonographically assessed tumours were correctly staged when compared with pathology results. In only three cases was the tumour understaged; it was overstaged in seven patients. Sensitivity of endorectal ultrasonography for detection of perirectal fat infiltration was 97 per cent, specificity was 90 per cent, negative predictive value was 98 per cent and positive predictive value was 90 per cent. Lymph node assessment was possible in 73 of 86 patients. In 13 cases local excision of the tumour did not allow a comparison of sonographic and histological findings. Lymph node involvement was accurately identified in 26 (76 per cent) of 34 patients by endorectal ultrasonography. Of 39 patients sonographically assessed to be without lymph node involvement, 32 were staged correctly and seven showed tumour infiltration (*Table 3*). The accuracy of prediction of lymph node involvement was 79 per cent. The sensitivity for predicting involvement was 78 per cent, specificity was 80 per cent, positive predictive value was 76 per cent and negative predictive value was 82 per cent.

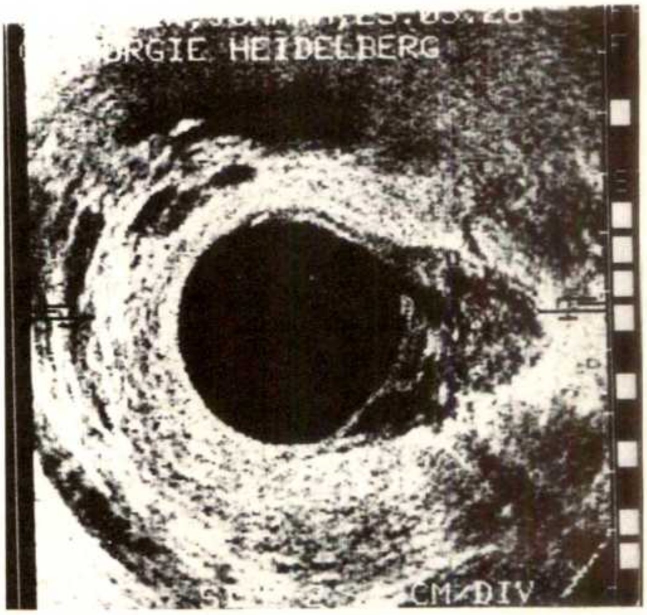

Figure 8 *Villous adenoma with malignant change indicated by the echo-poor spots within its substance*

Table 1 *Comparison of clinical staging and pathological assessment of tumour penetration depth (pT) in 61 patients*

	Pathological assessment			
Clinical staging	pT_1	pT_2	pT_3	pT_4
I	7	2	–	–
II	3	14	3	–
III	–	3	24	2
IV	–	–	1	2

Table 2 *Comparison of sonographic (uT) and pathological (pT) assessment of tumour penetration depth in 86 patients*

	Pathological assessment			
Sonographic staging	pT_1	pT_2	pT_3	pT_4
uT_1	12	2	–	–
uT_2	3	20	–	–
uT_3	–	4	36	1
uT_4	–	–	–	8

Table 3 *Comparison of sonographic (uLN) and pathological (pLN) assessment of lymph node involvement in 73 patients*

	Pathological assessment	
Sonographic assessment	pLN+	pLN–
uLN+	26	8
uLN–	7	32

Table 4 *Comparison of sonographic assessment of tumour penetration depth (uT) and pathological staging (pT) in 31 patients with villous adenoma*

	Pathological assessment		
Sonographic assessment	pT$_0$	pT$_1$	pT$_2$
uT$_0$	23	–	–
uT$_1$	2	4	–
uT$_2$	–	–	2

Assessment of villous adenomas

There were 31 patients with a primary diagnosis of tubulovillous adenoma of rectum. In 23 cases endosonography showed a villous adenoma with a homogeneous echo-rich pattern, but in eight cases a malignant change within the adenoma was detected by ultrasonography (*Table 4*). Six of these carcinomas were staged as uT$_1$ tumours and this was confirmed histologically in four cases. In two cases a uT$_2$ tumour was diagnosed and histological examination of the operative specimen confirmed infiltration of the muscularis propria in both.

Discussion

The choice of the therapeutic procedure in the treatment of rectal carcinoma is highly influenced by clinical and histopathological findings. The extent of direct local spread and the presence of lymph node involvement have usually been determined by direct palpation of the tumour and the rectal wall. Mason[14] published an accuracy of 70 per cent for those tumours that are confined to the mucosa and submucosa and an accuracy of 75 per cent for those that infiltrate the muscularis propria of the rectal wall. In the present study complete clinical staging was possible in 61 of 86 cases (71 per cent). Stage I was correctly staged in 78 per cent, stage II in 70 per cent, and stage III in 83 per cent; these figures are comparable to those published by other authors[14,15]. Nevertheless, reproducibility and reliability are dependent on the experience of the examiner. Furthermore, this method is limited to the distal 8–10 cm of the rectum. To perform a complete clinical staging it might not be sufficient just to touch the lower margin of the tumour. Thus, 20–30 per cent of tumours cannot be properly examined clinically.

Endorectal ultrasonography is a reliable means of preoperative assessment of the extent of a rectal tumour and its lymph node involvement. Considering the present results of preoperative assessment of small rectal carcinomas confined to the rectal wall and of villous adenomas, endorectal ultrasonography seems indispensible for the planning of sphincter preserving operations, especially local excisions. Sonographic assessment of perirectal fat infiltration had a sensitivity of 97 per cent, a specificity of 90 per cent and a negative predictive value of 98 per cent. In cases of uT$_2$ tumours, only three out of 23 were overstaged and not one was understaged in comparison with pathological assessment. Of 14 uT$_1$ tumours, two showed histological infiltration of the muscularis propria. These results are confirmed by other authors who have found accuracies of 85–100 per cent for the ability of endorectal ultrasonography to predict T$_1$ carcinomas[1,2,7,16]. Furthermore, results concerning the preoperative assessment of villous adenomas are encouraging. Out of 31 villous adenomas, six patients with malignant change were found by endorectal ultrasonography; no carcinoma remained undetected.

The main problem in staging rectal carcinoma by endorectal ultrasonography remains the difficulty in distinguishing between inflammatory and tumour-infiltrated tissue. In the present series this led to overstaging of three uT$_2$ tumours and four uT$_3$ tumours. One of the great advantages of endorectal ultrasonography is that the organs adjacent to the rectum can be clearly identified. Tumour infiltration in these organs can be detected with a high accuracy. About 10 per cent of such tumours are unfortunately accompanied by a high stenosis of the rectum which makes it impossible for the transducer to pass. To perform a complete staging by endorectal ultrasonography a residual lumen of 2 cm is necessary because only those structures seen at a 90° angle to the probe can be assessed correctly[4].

Table 5 *Accuracy of endosonography in predicting lymph node involvement*

	No. of patients	No. correct	Accuracy (%)
Saitoh *et al.*[7]	71	52	73
Hildebrandt *et al.*[12]	27	20	74
Rifkin and Wechsler[17]	81	70	86
Benyon *et al.*[18]	95	79	83

Four reports on the effectiveness of endorectal ultrasonography in the detection of mesorectal lymph nodes have been published[7,12,17,18]. The accuracies are shown in *Table 5*. The present results compare well with these reports, with an accuracy of 79 per cent. Sensitivity for prediction of positive lymph nodes was 78 per cent and specificity was 80 per cent. Echo-poor tumour-infiltrated and echo-rich inflammatory enlarged lymph nodes can be distinguished by endosonography, but unfortunately there are several kinds of transitional forms that make this difficult in some cases. In this series there were eight false positive and seven false negative results which are possibly the consequence of these transitional forms. Small lymph node size is another reason for the unsatisfactory results, because echodensity cannot be assessed in structures that are smaller than 0·5 cm. With the development and introduction of 10 MHz transducers, which have better resolution over short distances, it may be hoped that the results of predicting lymph node involvement will improve.

The possibility of performing a complete preoperative staging with assessment of the depth of tumour infiltration and of lymph node involvement has clinical relevance in four areas:

(i) In advanced tumours the relationship of the tumour to adjacent organs can be assessed and resectability can be estimated.
(ii) In T$_4$ and large T$_3$ tumours preoperative irradiation can lead to a reduction of tumour mass and the success of irradiation can be assessed by endorectal ultrasonography.
(iii) Patients with sonographically positive lymph node involvement may enter adjuvant therapy studies.
(iv) Endosonography may allow safer planning of local excision for villous adenomas and small rectal carcinomas.

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Short note

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Early incontinence following flexible sigmoidoscopy

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Flexible sigmoidoscopy is a well established out-patient procedure, requiring a simple enema bowel preparation, and is normally performed without intravenous sedation.

The potential advantage over rigid sigmoidoscopy is evident; 70 per cent of all colonic neoplasms occur within reach of the standard 60 cm instrument and, of those adenomas shown to contain foci of invasive malignancy, 94 per cent occur in the sigmoid or lower descending colons[1].

The procedure is safe with a low rate of colonic perforation in experienced hands but we have become increasingly aware of 'minor' complications in the early postinvestigation period. The possibility that patients may suffer incontinence led us to review the procedure with particular reference to the frequency of this complication.

Patients and methods

A total of 112 consecutive patients (median age 68 years, range 45–85 years, 64 men and 48 women) underwent day case flexible sigmoidoscopy in a designated unit following a single phosphate enema No patient complained of incontinence following the phosphate enema. All procedures were performed by one of two experienced endoscopists, aspiration of fluid and air was made on removal of the endoscope and on completion of the procedure patients were encouraged to open their bowels before leaving the department.

The patients were undergoing follow-up for colorectal carcinoma or adenoma, or investigation of lower gastrointestinal symptoms. No patient was being investigated for faecal incontinence

Within 2 weeks of the investigation patients were sent a symptom questionnaire, they were asked to record details of continence and mode of transport to and from hospital

Table 1 *Fluid or faecal incontinence in relation to age*

Age	Total	Number
45–65	37	12 (32)
66–85	58	18 (31)

Values in parentheses are percentages, $\chi^2 = 0{\cdot}02$

Results

Of the patients 95 (58 men, 37 women) returned completed questionnaires, a compliance of 85 per cent.

Incontinence of faeces or fluid was reported by 30 (32 per cent) and a further 32 (34 per cent) described incontinence of flatus only.

This was particularly distressing for the 17 (18 per cent) who were incontinent of fluid or faecal material before reaching home (14 of whom were using public transport)

There was no significant difference in rate of incontinence between the sexes (19 (33 per cent) men and 11 (30 per cent) women, $\chi^2 = 0{\cdot}1$) or between the young and elderly (*Table 1*).

All the participants said that they would be prepared to undergo repeat examinations in the future.

Discussion

Flexible sigmoidoscopy is generally a well-tolerated procedure and remains the investigation of choice for examination of the rectosigmoid. We were surprised to learn that such a high proportion of patients experienced incontinence. Those who suffered most were those who were incontinent before reaching home – many of whom travelled by public transport (bus in all cases).

It is evident that the combination of a phosphate enema and flexible sigmoidoscopy may result in troublesome incontinence following the procedure. Patients are now warned of this possible side effect prior to the examination, are advised to make suitable travel arrangements and are provided with pads to be worn following the examination.

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Low anterior resection of the rectum using a double stapling technique

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Using a double stapling technique in 30 patients, anterior resection of the rectum was attempted for low rectal carcinoma (n = *28*), *giant rectal adenoma* (n = *1*) *and radiation-induced rectal stricture* (n = *1*). *There were three emergency operations. The rectum was stapled transversely more than 3 cm below the tumour using the adjustable-angle linear stapler* (*Roticulator®*). *Colorectal or coloanal anastomoses were constructed using the EEA® circular stapler introduced* per anum *through the anorectal stump staple line. Ten coloanal and 19 low rectal anastomoses were achieved. A protecting transverse loop colostomy was fashioned in one patient with coloanal anastomosis who developed a vaginal tear during the procedure. In one patient technical failure necessitated conversion to abdominoperineal excision of the rectum. All staple rings and resection margins were intact and free from tumour. There were two clinical anastomotic leaks, both treated successfully with a defunctioning transverse loop colostomy. One patient developed a small infective pelvic haematoma 2 weeks after surgery which required drainage. Hospital stay ranged from 6 to 15 days* (*mean 8 days*). *Continence was normal in all patients at 8 weeks. One soft coloanal anastomotic stricture required dilatation. No recurrences have been detected during a follow-up of between 10 and 22 months.*

Keywords: Rectal carcinoma, anterior resection, stapler, anastomosis

The new technology of the circular stapler has been acknowledged as a significant advance in surgical gastroenterology[1–4]. These devices have facilitated anterior resection of the rectum, particularly low resection when a hand-sutured anastomosis may be tedious, time consuming and perhaps not achieved with confidence. Nevertheless their use may be marred by technical difficulties, especially in the insertion of the rectal or anal purse-string and by the size discrepancies of the rectum and colon. Knight and Griffen[5] were the first to propose a double stapling modification of the single circular stapler technique as described by Ravitch and Steichen[1]. They later reported encouraging results with this technique using TA55® and EEA® staplers (US Surgical Corporation, Norwalk, Connecticut, USA, and Auto Suture, Ascot, UK)[6], which have been confirmed by others[7–9].

The recent availability of an adjustable-angle linear stapler Roticulator® (US Surgical Corporation and Auto Suture) has added a new dimension to the double stapling technique, further facilitating low anastomosis. This report describes an experience with the first 30 patients using this new instrument.

Patients and methods

Twenty-eight patients with rectal cancer, one patient with a giant villous adenoma, and one with radiation-induced rectal stricture underwent curative surgery using this technique All the lesions were sited below the pelvic peritoneal reflection and were therefore at the mid or low rectal level. There were 14 men and 16 women of mean age 62 years (range 27–82 years) Three operations were done as emergencies for large bowel obstruction. In the elective cases, preoperative staging with chest radiography, abdominal ultrasonography and serum carcinoembryonic antigen measurement did not indicate distant metastatic disease in any of the patients. This was confirmed at laparotomy. The patient with the symptomatic radiation-induced rectal stricture had been treated by external beam therapy for carcinoma of the cervix 5 years previously but had no signs of recurrent disease at surgery. One man with a giant villous adenoma had an incomplete peranal excision during which rectal perforation occurred, thereby necessitating the anterior resection

For elective cases the bowel was routinely prepared with 4 litres polyethylene glycol orally on the day before surgery, the patient having had a fluid diet on the previous 2 days. The three patients who underwent emergency surgery had intraoperative antegrade colonic lavage to cleanse mechanically and to decompress the proximal colon before anastomosis[10] All patients were given prophylactic antibiotic cover.

The patient was placed in the Lloyd-Davies position for simultaneous access to the abdomen and perineum. Laparotomy was performed through a midline incision The sigmoid colon and rectum were fully mobilized to include division of the lateral ligaments to allow curative clearance of the mesorectum to the pelvic floor[11,12] At this stage the tumour was fully mobilized and an assessment was made of the feasibility of a curative anterior resection The Roticulator 55 (3·5 mm staples) was angled and locked at approximately 90° and a trial insertion on to the rectum was made below the tumour, at the same time applying strong upward traction on the rectum to maximize distal clearance. This could be facilitated further by an assistant applying upward pressure on the perineum from below Lateral pelvic tissues have a tendency to become incorporated in the jaws of the instrument and were avoided The vagina should also be drawn forward and upward with a deep pelvic retractor to prevent its incorporation in the staples If the distal clearance was judged adequate (at least 30 mm) the instrument was locked and fired. A right-angled light rectal occlusion clamp was applied above and the rectum was transected on to the edge of the Roticulator which was then released and removed It was helpful at this stage to apply long tissue forceps at either end of the staple line to demarcate and elevate it

The second stage of the restorative procedure was performed following full mobilization of the left colon and removal of the distal sigmoid and rectum, inclusive of tumour A 2/0 polypropylene purse-string suture was inserted at the proximal resection edge either manually or using the purse-string applicator (US Surgical Corporation and Auto Suture) and the lumen was measured and dilated to 28 or 31 mm using the obturators (US Surgical Corporation and Auto Suture). The anus was lubricated and gently stretched. A size 28 or

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31 mm EEA stapler was inserted *per anum* in the fully locked position without the anvil by an assistant. In only two cases was a size 25 mm EEA stapler used because of a very narrow colon. The shaft of the instrument was gently pushed upwards and through the centre of the Roticulator staple line, directed and assisted by the abdominal operator who made a small stab incision on to the blunt end of the shaft and between the staples. Once through, the shaft was fully extended and the anvil was screwed on. The distal colon was guided on to the anvil and the purse-string was tied. The perineal operator then screwed the anvil of the EEA on to the head while the abdominal surgeon checked that there was no intervening extraneous tissue caught up in the device. The instrument was fired, released and removed in the usual manner. The rings or 'doughnuts' were examined for completeness. The distal or rectal doughnut always had some Roticulator staples incorporated in it Although the anastomosis was not tested by intraoperative air or fluid insufflation, or by postoperative radiology, peranal palpation was always performed to ascertain a complete and intact staple ring. In no case was suture augmentation of the anastomosis attempted. One patient developed a vaginal tear during anastomosis which was repaired and protected with a transverse loop colostomy.

The anastomosis was routinely placed below the pelvic peritoneum and a small suction drain was left in the presacral space for 24–48 h, after lavage of the peritoneal cavity with 1 per cent tetracycline. The precise level of the anastomosis was determined by out-patient sigmoidoscopy at about 4 weeks after surgery

Results

There was no mortality and no wound infections occurred. Mean hospital stay was 8 days (range 6–15 days). After anastomosis all the anastomotic rings (doughnuts) examined were intact. Histopathology did not detect any tumour in these rings or in the resection margins of the complete specimen. Clinical anastomotic leaks occurred in one man and one woman. These two pelvic extraperitoneal dehiscences presented on the fifth and sixth day respectively with low grade fever, tenesmus and spurious diarrhoea. The diagnosis was confirmed by gentle digital examination. Treatment was by immediate loop transverse colostomy without full laparotomy. Both patients responded well and their colostomies were subsequently closed. The patient in whom a vaginal tear necessitated a protecting colostomy subsequently developed a small recto-vaginal fistula which was repaired. The patient who underwent excision of the villous adenoma was readmitted 2 weeks after surgery with pyrexia and was shown on ultrasonography to have a small pelvic collection. At laparotomy 30 ml infected haematoma was drained, after which his recovery was uneventful. One patient with a coloanal anastomosis developed a soft anastomotic stricture which required one dilatation under anaesthesia. In that patient a 25 mm EEA stapler had been used. The failure to perform low anterior resection in one patient occurred due to excessive tissue being incorporated between the head and the anvil. The anastomotic rings were incomplete. There was extensive tearing of the anal mucosa and sphincters, and palpation of the coloanal anastomosis revealed disruption. This was thought to have occurred due to an inadequately inserted EEA head which was caught at the level of the anal sphincters causing tissue disruption on closure and firing. Abdominoperineal excision was performed because of the severe sphincter damage in this elderly patient who might have become incontinent had reconstruction been attempted.

All patients had loose bowel motions with troublesome frequency of defaecation during their hospital stay. Some had urge incontinence. In most patients these symptoms improved with constipating agents such as diphenoxylate and atropine or loperamide. All had settled within 8 weeks. Follow-up has ranged from 10 to 22 months (mean 15·5 months). During this period no cancer recurrence has been detected. The sigmoidoscopic level of the anastomoses ranged from 3 to 7 cm from the anal verge (mean and median 5 cm). Ten of these anastomoses lay at 3 cm from the anal verge and were therefore classified as coloanal. Indeed, in several of these anastomoses, squamous epithelium was noted histologically in the distal doughnut.

Discussion

Stapled anastomoses in colorectal surgery are now widely acknowledged as safe and reliable with the instrumentation currently available. Such anastomoses may have advantages over hand-sewn anastomoses in certain situations[1–4]. The double stapling technique described above certainly allows ultra-low anastomoses to be constructed as demonstrated by the sigmoidoscopically determined level of the staple line. The use of the double stapling technique also lessens contamination as the rectum is not opened as it would be for a hand-sewn anastomosis or for the placement of the distal purse-string when the EEA alone is used. Exfoliated neoplastic cell implantation[13] in the pararectal tissues may also be diminished for this reason. Although we do not routinely practise rectal washout with a cytocidal agent before application of the Roticulator, it is possible that this manoeuvre may further reduce the incidence of anastomotic recurrence by prevention of tumour cell incorporation in the staple lines. The one patient in whom minor pelvic sepsis due to an infected haematoma occurred, despite satisfactory healing of the anastomosis, had a prior rectal perforation (and therefore contamination) during attempted peranal excision of a giant rectal adenoma. The Roticulator obviates the placement of the distal purse-string which, inserted by the abdominal or anal[14] approach, can be extremely difficult when the EEA alone is used in a low resection. Peranal insertion of the purse-string[14] or peranal coloanal anastomosis[15] causes prolonged stretching of the anal sphincters which may adversely affect the final functional result. The discrepancies in the size of the anorectal stump and the colon are no longer a problem with the double stapling technique. Bunching of excessive rectal tissue in the EEA can be a problem when the colon is of smaller size. Although we did not accurately record the duration of operation, in several patients the entire procedure was able to be completed within 1 h. This observation is in keeping with recorded time reduction by others[9].

The clinical anastomotic leak rate was 7 per cent, or 10 per cent if the patient with the vaginal tear is included. This is comparable with the reported leak rates of 5–18 per cent for low colorectal anastomoses using the EEA alone[16] and similar to those reported using a double stapling technique with fixed-angle linear staplers such as the TA55® or LS60® (US Surgical Corporation and Auto Suture)[6–9]. However, the range of anastomotic level from the anal verge reported in the present series (3–7 cm) is lower than that reported previously (3–12 cm) (Reference 9) and the results should be interpreted in that light. Furthermore, there have been no local recurrences to date, which compares favourably with other series[8]. In women coloanal anastomosis can be performed at the level of the levator muscles with traction on the rectum. In men the Roticulator can on occasion prove to be rather bulky for a narrow pelvis, precluding lower stapling

The cancer operation must never be compromised for convenience. Although satisfactory long-term results have been reported with clearance margins as low as 1 cm[8,17], a minimum longitudinal clearance of 3 cm together with the mesorectum is desirable[12,13,18]. This does not include the additional small clearance that the EEA doughnut adds to the distal resection margin. Although sphincter preservation should be avidly sought[13,18–20], abdominoperineal excision of the rectum must be performed when an adequate clearance cannot be assured. In particular, lateral clearance is of the utmost importance and must not be compromised[11,12,18,21].

There are certain technical pitfalls. Perforation of the anorectal stump by the shaft of the EEA can be prevented by adequate lubrication and insertion in the fully locked position guided by the abdominal operator. The perineum should be positioned just over the edge of the table so that vertical manipulation of the EEA is unhindered. The curved instrument facilitates this manoeuvre but it is not essential. Small EEA head sizes should be avoided because doughnuts are difficult to examine and stricture formation may be more likely. To avoid catching the EEA head at the anal sphincters, a gentle anal stretch before insertion is recommended. The shaft of the EEA may be inserted directly through the centre of the linear staple line of the Roticulator. This appears to offer support without tearing of adjacent tissue on closure of the instrument. It also results in the circular EEA blade having to cut through a lesser number of staples than it would if the shaft was introduced off-centre. The technique can be further refined by use of the new Premium EEA® (US Surgical Corporation and Auto Suture) instrument which has a pointed shaft that can be used to pierce the staple line easily. The shaft of this instrument does not snag on the rectal wall on insertion as the spindle on the conventional EEA tends to do. A further advantage is the completely detachable anvil which permits easier introduction of the proximal colon on to it and easier tying of the purse-string suture. Although the circular blade of the EEA is capable of cutting through the heavier wire gauge of the 4·8 mm staples, it is preferable to use the 3·5 mm Roticulator or TA instrument if possible (manufacturer's recommendation, personal communication) for the linear staple line This is even more important if the shaft is introduced off-centre as the EEA blade then has to cut through more staples than usual and failure may result in tissue tearing and hence a less secure anastomosis. The TA55 stapler is cheaper and may suffice in some situations, particularly in the wide female pelvis. In others, the narrower TA30® (US Surgical Corporation and Auto Suture) may enable stapling of the narrower anorectal junction although the authors have no experience of this. In the situation where these linear staplers cannot be used it should be remembered that a sutured coloanal anastomosis may be feasible[15], provided adequate clearance has been obtained

These early results appear promising. A safe low anastomosis was able to be achieved in the emergency situation and in the radiation-injured rectum. Some upset of the pattern of defaecation is to be expected but this appears to resolve in the fullness of time. The double stapling technique with the Roticulator appears to facilitate ultra-low anterior resection of the rectum with safety. The cancer operation is not compromised and the principles of sphincter preservation are not breached.

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Surgery for Crohn's disease in childhood: influence of site of disease and operative procedure on outcome

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Factors influencing outcome after surgery have been studied in 67 children requiring bowel resection or diversion of the faecal stream for Crohn's disease. Patients were divided into four groups on the basis of disease location at time of surgery, and mean follow-up was 4·5 years. All three children with panenteric disease (group 1) have relapsed. Best results were observed in cases with disease confined to the small bowel (group 2) and ileocaecal region (group 3), in whom surgery was followed by sustained remission in six out of seven and 24 out of 30 patients respectively. In the 27 children with colitis (group 4), results were mixed. Six of the seven patients who had staged colonic resections with a primary anastomosis relapsed, as did three out of four patients given a loop ileostomy to divert the faecal flow; in contrast, 15 out of 16 children who had a subtotal colectomy with ileostomy as the primary procedure have remained well, with only minor problems involving the rectal stump. An acceleration in growth velocity was observed during the first year after operation in 89 per cent of 40 children studied. Outcome after surgery for Crohn's disease in childhood depends mainly on disease location, but is influenced by the type of primary operation performed. In addition to symptomatic relief the principal early benefit of surgery is improved growth.

Keywords: Crohn's disease, surgery

Crohn's disease is uncommon in children, with an estimated prevalence of one case per 10 000 of the paediatric population[1]. Recent data suggest that Crohn's disease has increased in this age group over the past 30 years[2,3]. The disease often results in considerable morbidity and frequently requires surgical intervention, such as surgery to resect or bypass inflamed or strictured bowel or local surgery for the relief of complications such as perianal skin tags, fistulae and abscesses. There have been relatively few reports documenting the outcome of surgery in children. We, therefore, present a large retrospective study investigating outcome in 67 children who have required bowel resection or diversion of the faecal stream for complications of histologically proven Crohn's disease before their 17th birthday, with particular emphasis on the influence of disease location at the time of surgery and the type of operation performed, and the effect on growth in the first year after operation.

Patients and methods

Between 1975 and 1988, 167 children presenting to the Paediatric Inflammatory Bowel Disease Clinic at St. Bartholomew's Hospital, London have been diagnosed as having Crohn's disease. In each case, the diagnosis was established using a combination of clinical, radiological, endoscopic and histological criteria as described by Chong *et al.*[4]. Detailed information relating to the site, extent and severity of disease was documented.

Sixty-seven (40 per cent) of these children have required a total of 88 surgical procedures before their 17th birthday up to 31 December 1988. Ninety-one patients of the total series of 167 had passed the age of 17 years by that date, of whom 40 have required surgery (44 per cent). Detailed information about each patient was obtained retrospectively from the case notes and from computer-stored records. Data were collected concerning the child's sex, ethnic origin, source of referral, age at first presentation, age at first referral to St. Bartholomew's Hospital, number of preoperative admissions to hospital, age at surgery, disease location at the time of surgery, the type of operative procedure performed and clinical course after surgery. In addition, detailed auxological data (3-monthly height measurements) were available in 40 children for the 12-month periods before and after surgery, allowing the child's preoperative and early postoperative growth velocities to be calculated. All growth data had been recorded by a paediatric clinical auxologist.

Forty-four patients were male (35 gentile Caucasian, four Jewish Caucasian, three Indian subcontinent, two Afro-Caribbean) and 23 were female (17 gentile Caucasian, three Jewish Caucasian, two Afro-Caribbean, one Indian subcontinent). Nine children were resident in the North East Thames Regional Health Authority area at the time of presentation, while the remaining 58 were secondary or tertiary referrals. Mean age at first presentation to the general practitioner for the whole group was 9·8 years (range 2·0–15·7 years) and mean age at first referral to the Academic Department of Paediatric Gastroenterology at St. Bartholomew's Hospital was 11·2 years (range 3·2–16·0 years). The mean number of preoperative hospital admissions was 2·3 (range 1–8) and mean age at first operation was 13·6 years (range 6·1–16·9 years). All 88 operative procedures were performed under general anaesthesia, of which 79 involved bowel resection or diversion of the faecal stream (major procedures) and nine were for localized perianal disease (minor procedures). Endoscopic examinations of the bowel, whether under sedation or general anaesthesia, have not been included in the study.

The children were divided into four groups based on the main site of disease at time of surgery, as this was the major factor in determining the type of operation performed. Group 1 ($n=3$) consisted of children with panenteric Crohn's disease (major lesions scattered throughout the gastrointestinal tract). Children in group 2 ($n=7$) had diffuse small bowel disease, while those in group 3 ($n=30$) had disease localized to the terminal ileum or ileocaecal region. The remaining children in group 4 ($n=27$) had Crohn's colitis and were divided into three subgroups: perianal disease (4a, $n=4$), patchy colitis (4b, $n=7$) and diffuse colitis (4c, $n=16$). *Tables 1* and *2* show the sex ratio, ethnic origin, mean age at first presentation to the general practitioner, mean age at referral to St. Bartholomew's Hospital, mean number of preoperative admissions, mean age at time of surgery, and the total number of operations performed for each of the four main groups.

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Table 1 *Sex and ethnic origin of surgical patients according to site of disease at primary operation*

Group	Site of disease	No. patients	M/F	Gentile Caucasian	Jewish Caucasian	Indian subcontinent	Afro-Caribbean
1	Panenteric	3	1/2	3	0	0	0
2	Diffuse small bowel	7	6/1	4	1	1	1
3	Ileocaecal	30	18/12	26	0	1	3
4	Colonic	27	19/8	19	6	2	0

Table 2 *Age at presentation, hospital referral and time of surgery according to site of disease at primary operation*

Group	Site of disease	No patients	Mean age at first general practitioner visit (years)	Mean age at referral to St. Bartholomew's hospital (years)	Mean no preoperative admissions	Mean age at surgery (years)	No. operations
1	Panenteric	3	11·2	14·1	5·0	15·1	14
2	Diffuse small bowel	7	9·8	10·3	2·3	13·2	8
3	Ileocaecal	30	10·7	11·4	1·9	14·1	31
4	Colonic	27	8·1	9·1	2·4	12·3	35

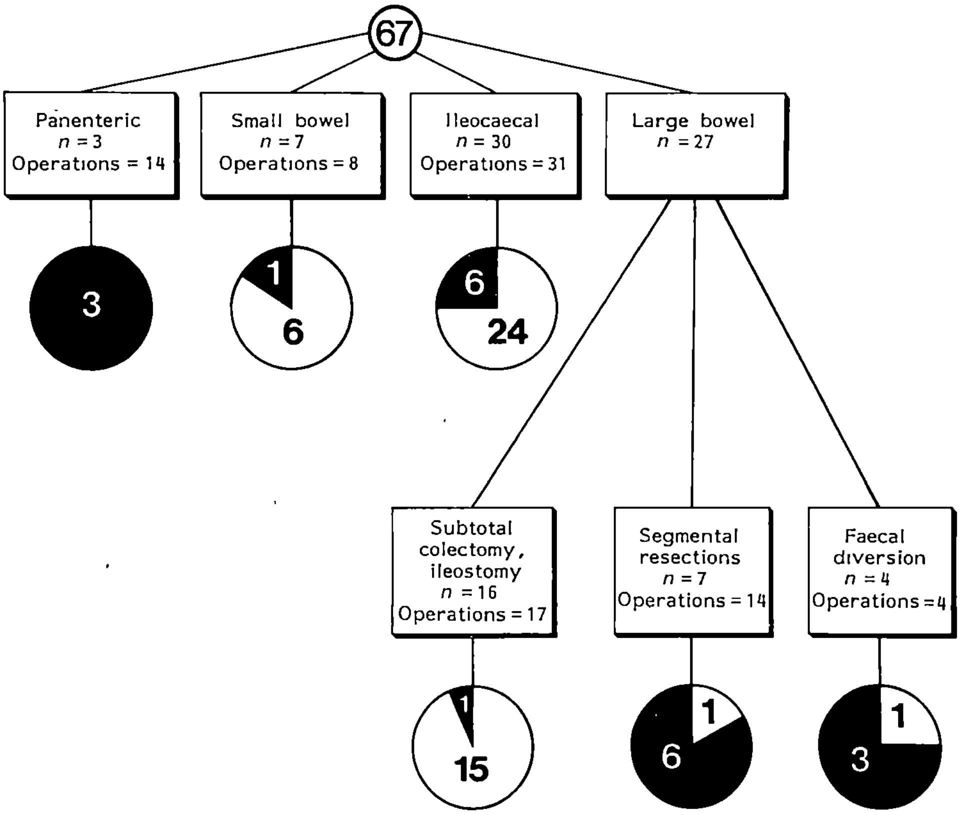

Figure 1 *Outcome following surgery for Crohn's disease in 67 children grouped according to site of disease at time of primary operation* ○, *Good outcome,* ●, *poor outcome*

All operative procedures reported in this study were performed by the same surgical firm and the mean duration of follow-up for the group was 4·5 years

Student's *t* test was used to calculate the level of statistical significance of the mean change in growth velocity after surgery for each disease group. A P value $<0{\cdot}05$ was considered significant.

Results

Results after surgery for each anatomical group are shown in *Figure 1*. Outcome relates to the primary operation and has been classed as 'good' or 'poor' according to the following criteria. Good outcome indicated remission of disease requiring no further surgery and independence of medical therapy (steroids, elemental diet) to maintain remission. Poor outcome indicated proven disease recurrence requiring further surgery after the primary operation, or dependence on continuing medical therapy (steroids, elemental diet)

The overall relapse rate after surgery was 30 per cent at a mean follow-up interval of 4·5 years after the primary operation. There has been no mortality in any of the four groups.

Group 1· panenteric disease (n = *3*)

The main indications for surgery in this group were failure of medical treatment to control symptoms and perianal complications. Fourteen operative procedures (six major, eight minor) have been required to date. One child underwent a right hemicolectomy for a stricture in the terminal ileum and has remained well, but is dependent on medical therapy. A second child had a small bowel resection, then a right hemicolectomy, then a left hemicolectomy with a colostomy and mucous fistula, and later developed a rectovaginal fistula. The remaining child has had local surgery for severe perianal disease, followed by a defunctioning loop ileostomy and finally an abdominoperineal excision of the rectum for continuing perianal disease and rectovaginal fistula. Morbidity has been very high in this group.

Group 2: diffuse small bowel disease (n = *7*)

The main indications for surgery were acute or subacute bowel obstruction, or chronic abdominal pain without evidence of obstruction. Four patients had a segmental jejunal resection as the primary procedure and the remaining three had segmental jejunal resection combined with a right hemicolectomy. Follow-up has ranged from 18 months to 6 years. Six of the children have remained well. One child relapsed (not at the primary anastomosis) and has required further small bowel surgery. Morbidity has been low in this group.

Group 3: terminal ileal and ileocaecal disease (n = *30*)

The main indications for surgery were stricture formation in the terminal ileum and/or growth failure despite intensive medical treatment. All children in the group underwent a right hemicolectomy and 24 (80 per cent) are well, asymptomatic, and requiring no medical treatment at a mean follow-up interval of 4·4 years (range from 7 months to 9 years). Six patients have had radiologically proven small bowel recurrence, of whom one has required further surgery (jejunal resection) 5 years after the primary operation. Again, morbidity has been low.

Group 4: Crohn's colitis (n = *27*)

Group 4a: severe perianal disease (n = *4*). The four children in this group had severe, chronic perianal disease and had a defunctioning loop ileostomy in an attempt to heal the perineum. The results were disappointing. Only one child benefited and little or no improvement was observed in the other three.

Group 4b: patchy colitis (n = *7*). The children in this subgroup underwent a partial resection of the colon as the primary procedure. The mean follow-up period to date is 5·5 years (range from 8 months to 7 years). One child had an extended right hemicolectomy, but developed disease in the remaining colon after 6 years. A second child had a subtotal colectomy with an ileosigmoid anastomosis, but within 3·5 years developed severe anastomotic and small bowel ulceration necessitating a sigmoid colectomy, ileostomy and mucous fistula. A third child had a right hemicolectomy as the primary procedure, but subsequently developed a recurrence at the anastomosis. Another child in this group had a left hemicolectomy, followed by a right hemicolectomy with an ileosigmoid anastomosis, and after 5·5 years of follow-up has developed severe small bowel disease. A fifth child underwent a right hemicolectomy, then a left heimcolectomy, then a subtotal colectomy with an ileostomy and mucous fistula but developed severe disease in the ileostomy stoma. A sixth child had a sigmoid colectomy, then required a right hemicolectomy and finally a proctocolectomy with ileostomy. The remaining child underwent colectomy with an ileorectal anastomosis recently and, although currently well, is still in the early postoperative period. The morbidity in this subgroup has been high. Four patients have required further surgery and the total number of operative procedures to date is 14. All but one retained their rectum, but five of the six have active Crohn's disease in the rectal stump.

Group 4c: diffuse colitis (n = *16*). All of the children in this subgroup had a subtotal colectomy, ileostomy and mucous fistula as the primary operative procedure. Fifteen children have remained well at a mean follow-up interval of 5·2 years (range from 14 months to 9 years), although all have evidence of disease activity in their rectal stump Only one child has required further surgery for a severe small bowel recurrence 5·5 years after the initial operation. The morbidity in this subgroup has been low

Influence of surgery on growth

The results of surgical intervention on growth during the first year after operation are shown in *Table 3* for the 40 children in whom detailed auxological data were available. Because of the small numbers involved, data from groups 4b and 4c (subtotal colectomy with or without ileostomy) have been combined; there were no significant differences in the means of the growth velocities before and after operation between the two groups. Insufficient growth data were available for analysis from groups 1 and 4a.

Eighteen (45 per cent) of the 40 children were below the third centile for height at the time of operation, demonstrating that growth retardation was a major problem. In each disease group there was a significant increase in the mean growth velocity in the first year after surgery of between twofold and threefold ($P < 0.001$). Eighty-nine per cent of all children demonstrated an acceleration in growth velocity, which was twofold or greater in 69 per cent.

Discussion

Farmer and Michener[5] found that 69 per cent of 522 patients with Crohn's disease with onset before 20 years of age required surgery within a mean period of 7·7 years from diagnosis, although the need for surgery was unrelated to disease location. Puntis *et al.*[6] recorded a high incidence of surgery in 67 cases of children with Crohn's disease, with 87 per cent requiring some form of surgical procedure during an average follow-up period of 16 years. In the present study, surgery was necessary before the 17th birthday in 44 per cent of the children who had passed this age.

Interpretation of the outcome after surgery demands careful classification of patients into broadly comparable groups, as the disorder causes a wide variety of lesions and complications which may vary between patients. Gryboski and Spiro[7] used

Table 3 *Effect of surgery on growth velocity in 40 children grouped according to disease location at time of primary operation*

Site of disease	No. patients	No. <3rd centile	Mean age at surgery (years)	Growth velocity* Before surgery (cm/year)	Growth velocity* After surgery (cm/year)	Percentage with increase in growth velocity	Percentage with >twofold increase in growth velocity
Diffuse small bowel (group 2)	6	2	14·5	2·77	7·28	83	67
Ileocaecal (group 3)	20	9	14·3	2·72	6·92	88	65
Colonic (group 4b + 4c)†	14	7	13·4	1·92	7·44	92	77
Total	40	18	14·0	2·45	7·16	89	69

* Growth velocity has been calculated for a minimum of 12 months before and after surgery; † growth data from groups 4b and 4c have been combined

'site of disease' to classify patients in a 10-year retrospective study of long-term prognosis in 86 patients. Those in group 1 had diffuse small bowel disease and those in group 2 had terminal ileal disease only; surgery was required in these children mainly for obstructive symptoms. Children in group 3 had ileocolonic disease and those in group 4 had colitis only; surgery was performed in these patients for a variety of complications. Fifty-five per cent of the 45 children with ileocolonic disease required some form of bowel resection, of whom 15 required further surgery for disease recurrence. We adopted a similar scheme of classification.

Mortality from surgery was zero but morbidity varied considerably. Surgery was very successful in children in group 3, as demonstrated by immediate relief of symptoms and a sustained remission and growth acceleration in the majority. Surgery was also successful in group 2 for the relief of obstructive symptoms and to promote growth. Disease recurrence leading to further stricture formation causes concern because of limitations in the amount of small intestine that can be resected. In Crohn's colitis, subtotal colectomy with an ileostomy, mucous fistula and preservation of the rectal stump appears to be the operation of choice, improving the child's clinical condition and growth in the short term. Closure of the ileostomy by ileorectal anastomosis at a later date remains possible. In contrast, staged, segmental resections of the colon in this series were almost invariably followed by early disease recurrence, often at the site of anastomosis. There was an improvement in short-term growth rate during the period of remission. Diversion of the faecal flow via a loop ileostomy for the treatment of severe perianal disease was generally unhelpful and is not recommended[8,9]. In children with panenteric Crohn's disease the results of surgery are likely to be disappointing and medical therapy remains the mainstay of management. Surgery has an important role in dealing with perianal complications.

Between 20 and 30 per cent of children with Crohn's disease have suboptimal growth[10,11], often accompanied by a significant delay of puberty. Linear growth impairment may even precede symptoms and can be the earliest indication of disease[12]. The mechanisms responsible for growth retardation are not well understood but probably include an inadequate calorie intake secondary to anorexia[13,14], malabsorption of food[15], chronic inflammation in the bowel ('toxic mass'), secondary endocrine disturbances[16] and long-term corticosteroid therapy. An aim in managing these children must be to promote an acceleration in growth rate sufficient to return the child to the same percentile as before the illness. Evidence is conflicting on the effects of surgery[17,18] but our data suggest benefit, at least in the short term.

A combined approach to managing children with Crohn's disease, involving both surgeon and paediatrician, may be of importance when deciding on the optimum time for surgery, in preparing the child for operation, in assessing the extent and severity of disease in the operating theatre and in the postoperative management, with particular regard to medical therapy and growth.

The efficacy of surgery for Crohn's disease in children seems to depend mainly on disease location and may be influenced by the surgical procedure. In addition to symptomatic relief a benefit of surgery is an acceleration in growth velocity. Surgery is not a cure for Crohn's disease but, when timed correctly, may be rewarding in the management of this most distressing disorder in childhood.

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Ambulatory anorectal physiology in patients following restorative proctocolectomy for ulcerative colitis: comparison with normal controls

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The purpose of this study was to determine the manometric activity of ileoanal W pouch reservoirs following restorative proctocolectomy for ulcerative colitis and to compare the results with normal controls. Thirty-one studies were carried out; there were 15 controls (median age 52 years (range 29–80 years), 10 men, 5 women) and 16 pouch patients (median age 40 years (range 28–52 years), 13 men, 3 women). Mid-anal sphincter pressure and 'rectal' pressure were measured with a microtransducer catheter. The signals were digitalized and recorded in a portable electronic memory for later computer display and analysis. The system allowed the study of patients with minimal constraints while fully ambulant. The frequency of sampling (rectal pressure ≥ sphincter pressure), sensation of flatus present and flatus being passed were 7(1–41), 3(1–7) and 1(0–3·5) per hour in the normal controls and 0(0–3), 0(0–1) and 0(0–1) respectively per hour in the pouch patients ($P < 0.001$)*. Compared with the highly dynamic nature of the anorectum in normal subjects the patients with a pouch had very little activity. The sensation of pouch filling and the desire to defaecate were noted on 12 occasions and in six were associated with a rise in pouch pressure greater than 20 mmHg. One patient had nocturnal soiling and this was the only patient in whom frequent pouch contractions were noted. The results suggest that ileoanal pouch motility is usually quiescent and that incontinence in this group may be related to increased pouch activity.*

Keywords: Ambulatory, anorectal physiology, ileoanal pouch

We have previously described a new technique for studying anorectal physiology in ambulant subjects[1]. This allows the patients to be observed in much more physiological conditions than previously and over relatively long periods of time. The purpose of the present study was to compare the results of anorectal manometric activity in normal controls with the neorectum following restorative proctocolectomy and ileoanal pouch anastomosis

Patients and methods

Patients

There were 31 subjects, 15 controls and 16 patients with a pouch (control m.f = 10·5, median age 52 years (range 29–80 years); pouch m:f = 13:3, median age 40 years (range 28–52 years)). Thirteen control subjects were waiting for surgery unrelated to the alimentary tract and two were taken from the colonoscopy follow-up waiting list having had a right-sided polyp removed 6 months previously and a normal colonoscopy within 2 weeks of the study. There were no dietary restrictions The pouch group were all consecutive patients attending the Bristol Royal Infirmary who had severe ulcerative colitis necessitating total proctocolectomy Ethical permission for the study was granted by the Bristol and Western Health Authority and all patients gave informed consent.

Methods

Surgery After total proctocolectomy a W pouch was fashioned as described by Nicholls and Pezim[2] except the pouches were constructed using a single layer of continuous 3/0 Vicryl® (Ethicon, Edinburgh, UK) In one patient, the anastomosis was performed at the line of the anal valves and in the rest the anastomosis was fashioned preserving 1 cm of transitional zone above the dentate line. The endoanal anastomosis was constructed using interrupted 2/0 Vicryl All patients had a covering loop ileostomy which was closed approximately 8 weeks after surgery. The median duration of follow-up was 21 months (range 12–32 months)

Ambulatory manometry. The technique has been described in detail previously[1]. In brief, a soft, flexible microtransducer catheter, 2 mm in diameter was used (16C/Sil 3, Gaeltec Ltd , Isle of Skye, UK) to measure pressure in the middle of the manometrically-defined sphincter and 6 cm proximally in the rectum It was connected to a portable box of electronics (Motility Digitrapper, Synectics Medical, Stockholm, Sweden) which allowed 3 h of recordings from two pressure channels to be stored in a digital memory. The box had an event marker button to enable the subject to mark on the trace any event which they felt It was calibrated using a pressurized chamber connected to a mercury manometer and zeroed at atmospheric pressure The catheter was then strapped to the natal cleft with adhesive tape up to the anal verge. The Digitrapper was positioned at the subject's waist on a belt and he or she familiarized with the use of the event marker. Both groups were asked to note and mark the sensations of the presence and passage of flatus In addition the pouch patients were requested to note all other sensations from the pouch such as filling and the desire to defaecate They recorded details of their activities on a notepad so that these could be related to the traces of pressure change.

Preliminary investigations using this technique revealed a very characteristic trace when subjects walked and these sections were excluded from the analysis to reduce possible error due to catheter displacement.

At the end of the study period the information was offloaded onto a computer (Type 1512, Amstrad, Brentwood, UK) which with the appropriate software (Motiligram, Synectics Medical) allowed the traces of pressure change to be displayed

Statistical analysis The data are expressed as medians with ranges in parentheses. All intergroup comparisons were analysed using the Mann–Whitney *U* test

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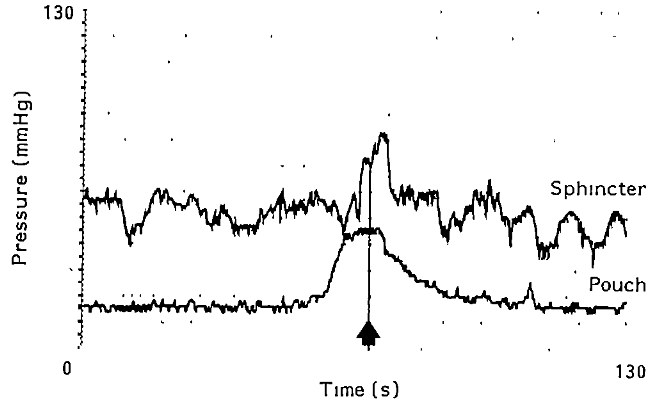

Figure 1 *The sensation of pouch filling was felt at the point marked (arrow). It is accompanied by a rise in pouch pressure and a 'covering' rise in sphincter pressure*

Results

Clinical outcome

Half the patients were on steroids at the time of pouch surgery. The median frequency of evacuation of the pouch during the day was 4 (range 3–6) and none had to evacuate at night. All but one patient had perfect continence. The exception was a 66-year-old woman who had nocturnal soiling and wore a pad at night. One patient had significant pelvic sepsis with an anastomotic breakdown necessitating pelvic drainage but eventually had a reasonable result in that he was fully continent and evacuated five times a day. Three patients had episodes of small gut obstruction and of these one required a laparotomy to divide adhesions. One patient had an anastomotic stricture requiring dilatation and another developed mild pouchitis treated successfully with metronidazole.

Ambulatory manometry

The median duration of the studies was 2·8 h in the controls and 2·7 h in the pouch group. In controls the most notable feature was the dynamic nature of the sphincter with numerous falls in sphincter pressure such that it was equal to or less than rectal pressure. Equalization of the two pressures occurred seven times per hour (range 1–41) of which 60 per cent were not felt by the subjects. The traces as a whole showed considerable variation in sphincter pressure such that there were many other falls in sphincter pressure that did not result in equalization with rectal pressure. Slow wave activity was seen in ten subjects.

Conscious sensory awareness of the presence of flatus in controls was noted three times per hour (range 1–7 per hour). It was associated with a fall in sphincter pressure of 30 mmHg (20–50 mmHg) which was equal to or lower than rectal pressure on 80 per cent of recorded occasions. Flatus was passed once per hour (0–3·5) and was usually associated with a fall in sphincter pressure (median sphincter pressure fall 35 mmHg, rectal pressure rise 8 mmHg).

In contrast with the highly dynamic sphincter in normal subjects the traces of pressure change in the patients with a pouch were relatively quiescent. The pressure in the anal canal and pouch exhibited little spontaneous variation although slow wave activity was seen in half the patients. Sampling, the sensation of flatus and flatus being passed were all rare events (hourly frequency: 0(0–3), 0(0–1), 0(0–1) respectively, $P<0.001$ compared with controls). On the single occasion that flatus was said to be felt and passed no change in pouch or sphincter pressure was recorded.

Sensory awareness of pouch activity was noted on 12 occasions. In six of these it was accompanied by a rise in pouch pressure which was greater than 20 mmHg and the patient felt that the pouch was filling in three (*Figure 1*); in the other six there was no discernible change in either pouch or sphincter pressure.

A total of 30 contractions of the pouch was recorded but these were limited to five patients. Seventy per cent of these were recorded from one patient who initially had a poor result with nocturnal soiling and had quite regular contractions at a rate of seven per hour. These were not associated with frank faecal incontinence but two were felt as a threat to continence and were accompanied by contractions of the external sphincter, possibly to prevent faecal leakage (*Figure 2*).

Contractions of the external sphincter (characterized by a very rapid rise and fall in pressure) were frequent in the pouch group (two per h, range 0–9). For the most part they were unrelated to any recorded sensory stimulus or change in pouch pressure (*Figure 3*). On several occasions, however, they were associated with pouch contractions (*Figure 4*). Such contractions were only seen in the control group in one subject when the rectum filled in the second half of the study period and then followed sampling episodes.

Discussion

Anorectal continence is dependent on the interaction of many factors. The anal sphincters, either by creating a pressure barrier or resisting stretch, and the compliant reservoir of the rectum are of prime importance. Anorectal sensation permitting the awareness of the presence and nature of rectal contents plays a significant role in the mechanism[3–5].

The complexity of the interaction between these factors is highlighted in this study, which has revealed striking differences in anorectal activity following the formation of an ileoanal pouch while preserving continence largely unchanged. The two groups, however, had to cope with very different threats to continence. The control subjects had to make the frequent distinction between solid stool and flatus, allowing the latter

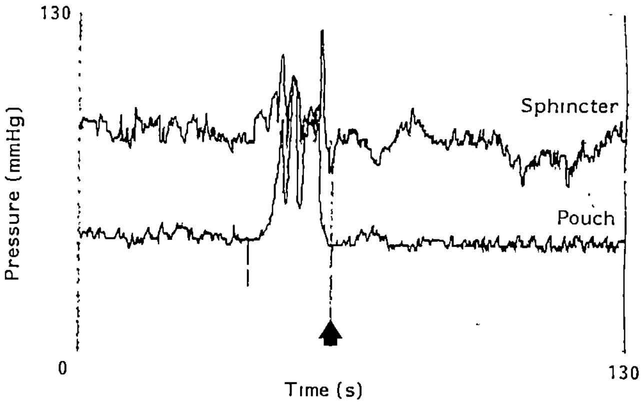

Figure 2 *In this example a series of powerful pouch contractions was felt by the patient as a threat to continence and was followed by a voluntary sphincteric contraction*

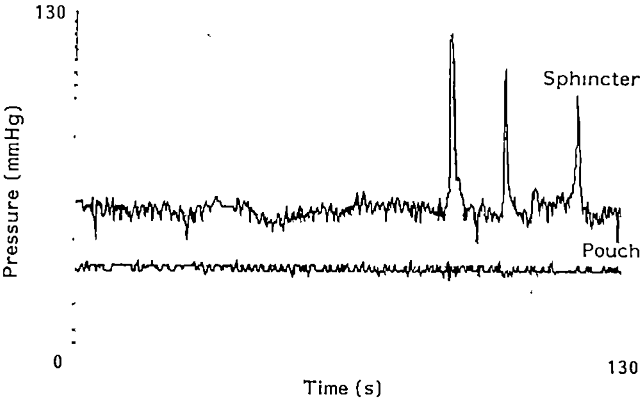

Figure 3 *Contractions of the external sphincter were frequent in the pouch group and were often unrelated to any sensory event or pouch contraction*

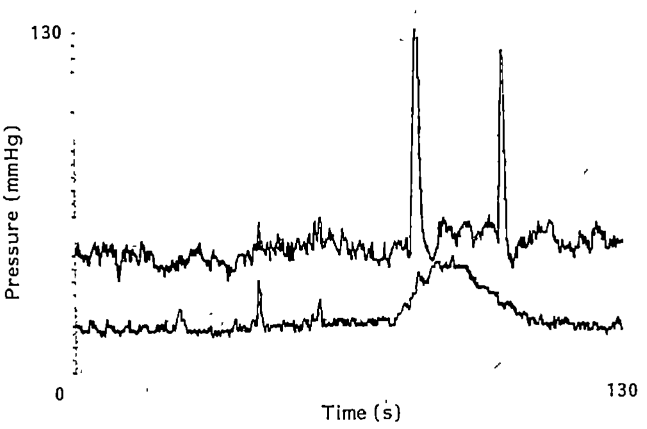

Figure 4 *Occasionally pouch contractions were accompanied by contractions of the sphincter, perhaps as a mechanism to prevent faecal leakage*

to be passed but retaining the former. This discrimination in normal controls is to a large extent dependent on the sampling reflex and therefore anal sensation[1,5]. The pouch patients passed little or no flatus presumably as a result of the colectomy and therefore hardly ever had to make this distinction.

This is relevant to the construction of the pouch as considerable controversy surrounds the question of the level of ileoanal anastomosis and whether to retain any mucosa above the line of the anal valves. The anatomy of this zone is extremely variable being made up of columnar epithelium near the anorectal junction and separated from the squamous epithelium at the approximate line of the valves by a zone resembling transitional epithelium, often called the anal transition zone[6–8]. It is highly sensitive[9,10] and several groups have demonstrated that normal anal sensation can be preserved if the transition zone is retained[11,12]. Furthermore, there are reports that if the anal transition zone is retained postoperative continence is improved[13,14]. This finding, however, may be due to higher resting sphincter tone[14] as the techniques which preserve the anal mucosa can involve less anal retraction.

Malignant change in remnants of columnar epithelium is the principal reason for the excision of all mucosa above the valves and while little inflammatory change has been noted in the transitional epithelium[15] some have argued strongly that all the anal mucosa above the line of the valves should be excised as dysplasia and even frank carcinoma can be missed[16]. Keighley *et al* called into question the clinical benefit of leaving the upper anal mucosa. They could not detect differences between six patients in whom it was retained and a larger group in which it was excised[17].

The conspicuous absence of pouch–anal sampling following endoanal anastomosis implies that it is unlikely that anal sensation plays as important a role in these patients compared with normal controls. Following colectomy the patients passed very little flatus and what was passed was usually at the end of emptying the pouch so that the distinction between gas and fluid stool was seldom necessary.

The lack of recordable pouch activity for much of the time was interesting. Stryker *et al.*[18] studied ileal pouch physiology in laboratory conditions over 24 h and described more frequent pouch waves (four per hour) particularly in the period preceding evacuation. This may be a reflection of the fact that most of their patients had a J pouch with a smaller capacity than the W type in this study. Their finding of increased activity before defaecation does raise the possibility that increased pouch activity in our patient with nocturnal faecal soiling may be secondary to incomplete emptying rather than any primary ileal abnormality. The association between frequent pouch contractions and incontinence does, however, raise the possibility that the outcome in such patients could be improved in future by drugs which selectively inhibit small gut activity.

The numerous contractions of the external sphincter in the pouch group was unexpected. Most were unrelated to any perceived threat to continence but several were closely associated with pouch contractions and on two occasions the pouch contraction was felt. These contractions may, therefore, represent a protective reflex to prevent soiling. More prolonged and detailed studies are currently underway to investigate this possibility.

Acknowledgements

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Fistulotomy without external sphincter division for high anal fistulae

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Thirty-two patients with high trans-sphincteric or suprasphincteric fistulae underwent fistulotomy without external sphincter division. Fifteen patients had posterior fistulae involving the deep postanal space and 17 patients had anterior fistulae. Primary healing, after removal of the seton, occurred in 25 of the 32 patients (78 per cent). Primary healing in patients with posterior fistulae occurred in 66 per cent and in 88 per cent of patients with anterior fistulae. Following surgery, eight patients (33 per cent) reported problems controlling flatus, six patients (25 per cent) reported mucous discharge and one patient (4 per cent) complained of occasional incontinence for liquid stool. No patient experienced problems controlling solid stool nor did any patient require the use of a protective pad. These results have encouraged us to use this method as the initial procedure of choice for these more difficult fistulae. A significant number of patients can be cured of their fistula while preserving the external sphincter, thereby minimizing the impact of surgical therapy on continence.

Keywords: Anal fistula, rectal surgery

Traditionally, a 'lay open' fistulotomy has been the treatment of choice for the majority of anal fistulae. For the intersphincteric and low trans-sphincteric fistulae, this technique generally corrects the fistula while maintaining continence. If this technique is applied to the high trans-sphincteric or suprasphincteric fistula, significant alterations in continence frequently result. Parks and Stitz, in 1976, described a method in which a portion of the external sphincter was preserved[1] and their initial results were encouraging. This report describes our results with a modification of their technique.

Patients and methods

Between July 1982 and July 1988 one author (H.L.K.) treated 176 cryptoglandular anal fistulae. Primary rectovaginal fistulae and fistulae associated with inflammatory bowel disease, hidradenitis or presacral developmental cysts were excluded. Recurrent anal fistulae referred from other institutions were included. The fistulae were classified according to the classification of Parks *et al*[2]: A, intersphincteric; B, trans-sphincteric, C, suprasphincteric; and D, extrasphincteric. The trans-sphincteric fistulae were further classified as 'high' or 'low'. 'High' trans-sphincteric fistulae involved approximately 50 per cent or more of the external sphincter mechanism posteriorly or 30 per cent or more of the external sphincter mechanism anteriorly. This subclassification based on 'percentage of muscle involved' is arbitrary and varies, depending upon the observer.

The majority of patients had either intersphincteric or low trans-sphincteric fistulae and underwent a 'lay open' fistulotomy. Thirty-two patients had 'high' trans-sphincteric or suprasphincteric fistulae. These patients were placed in the prone jack-knife position. Formal bowel preparation was not used. The external opening was identified, probed and the skin and subcutaneous tissue overlying the tract were opened from the external opening to the edge of the external sphincter. Any associated side tracts were unroofed (*Figure 1*). The internal opening was then identified and an internal sphincterotomy performed (*Figure 2*). Occasionally, a direct communication was not found because the intermuscular abscess did not penetrate the internal sphincter. By palpation, gentle probing and the use of Goodsall's Rule[3] the location of the offending glandular infection was usually determined and an internal sphincterotomy carried out in this location. The tract through the external sphincter was then readily identified and, once the intermuscular space had been exposed, the location of the tract through the external sphincter identified, and the amount of involved sphincter muscle assessed, a #1 silk suture was passed around the external sphincter and tied loosely (*Figure 3*). If a superior extension was present in the intermuscular plane, this was managed by extending the sphincterotomy incision in a superior direction. If a superior extension was present in the ischiorectal space this was managed by enlarging the tract sufficiently to obtain good drainage. The extension was curetted but packs were not used. Earlier the majority of patients were admitted on the day of surgery and discharged the following day. Currently, most of these procedures are performed on an outpatient basis. Postoperative management consists of routine Sitzbaths and bulk agents.

The wounds are followed in the outpatient department. If the fistula was associated with a high extension in the deep postanal or ischiorectal space, these wounds were examined under anaesthesia approximately 7–10 days after the initial procedure. Once significant healing had taken place and only a small tract corresponding to the location of the seton

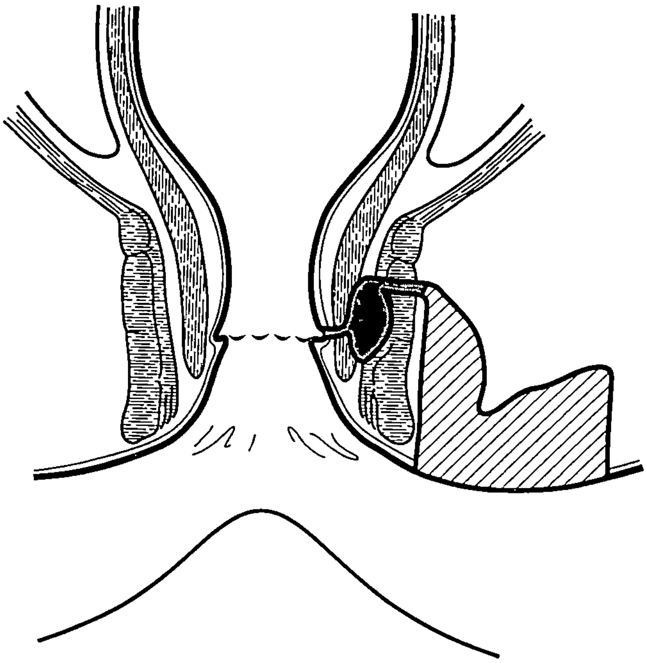

Figure 1 *Opening side tracks external to the sphincter*

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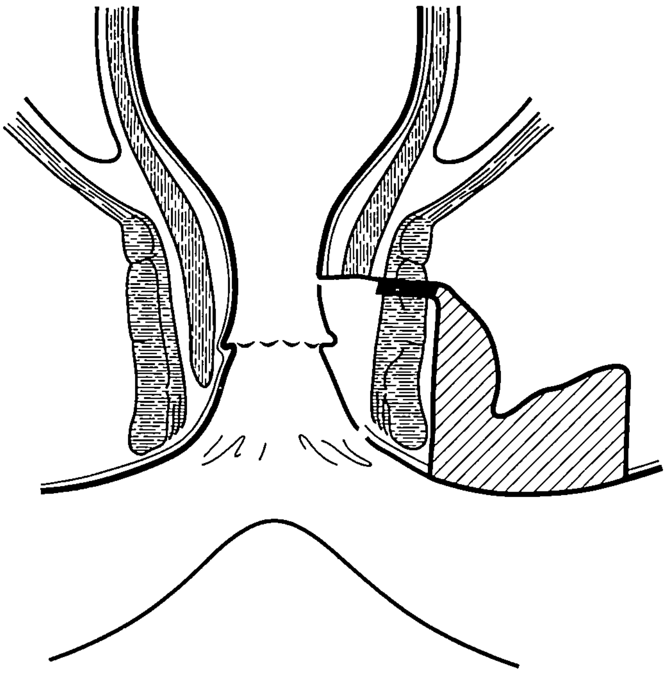

Figure 2 *Internal sphincterotomy*

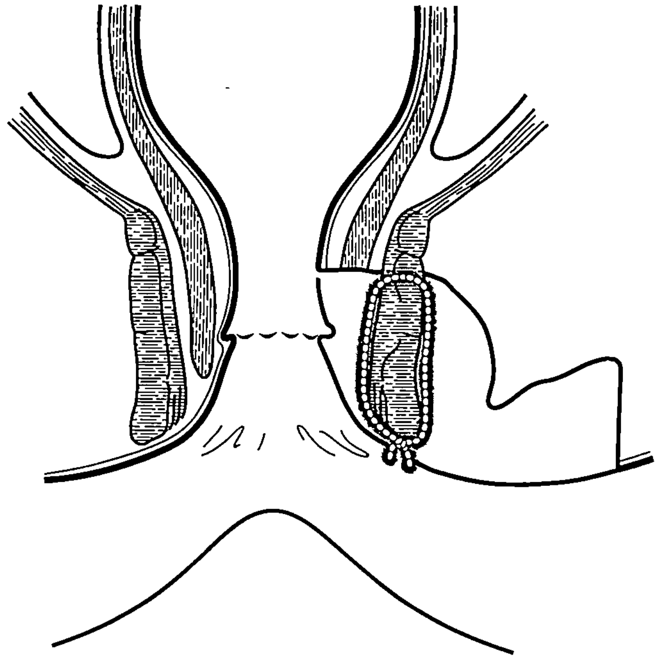

Figure 3 *Placement of seton*

remained around the external sphincter, the suture was simply cut and removed (*Figure 4*). Sitzbaths were continued and the patient followed until healing of the residual tract was complete

Persistent fistulae were defined by failure of the residual tract to heal within 4 months after removal of the seton Recurrent fistulae were defined as recurrent drainage after apparent healing of the residual tract.

Of the 32 patients treated utilizing the criteria and technique described above, there were 19 men and 13 women whose ages ranged from 25 to 77 years (mean age 46 years) In 15 patients, the fistulae arose in the posterior midline and involved the deep postanal space. The remaining 17 patients had anterior fistulae. One patient had a coexisting rectovaginal fistula secondary to the spontaneous rupture of the initiating perirectal abscess. Six patients had undergone one previous attempt at definitive fistula repair, while three patients had each undergone three separate attempts at definitive fistula repair. During anaesthesia, separating patients with very high trans-sphincteric fistulae from patients with suprasphincteric fistulae can be impossible Using the 'seton as a marker' as described by Goligher[4], it was felt that in the 15 patients with posterior fistulae, 13 had high trans-sphincteric fistulae and two patients had suprasphincteric fistulae. No attempt was made to subdivide the anterior fistulae into trans-sphincteric or suprasphincteric varieties.

The interval between fistulotomy and removal of the seton ranged from 2 to 17 weeks (mean 7 weeks). The interval between removal of the seton and complete healing ranged from 2 weeks to 16 weeks (mean 7 weeks)

Follow-up was obtained in 31 of 32 patients (97 per cent) and was accomplished by either outpatient evaluation (12 patients) or mailed questionnaire (19 patients). Follow-up ranged from 13 months to 65 months (mean 36 months).

Results

Primary healing, after removal of the seton, occurred in 25 of 32 patients (78 per cent). In patients with posterior fistulae (15 cases), primary healing occurred in 10 (66 per cent). In patients with anterior fistulae (17 cases), primary healing occurred in 15 (88 per cent). Overall, the fistula persisted in six patients and recurred after apparent healing in one patient. The persistence and/or recurrence rate for posterior fistulae was 34 per cent and for anterior fistulae was 12 per cent. One of the suprasphincteric fistulae was treated successfully by this method, while the other suprasphincteric fistula persisted.

Four of the seven patients in whom the fistula persisted or recurred were treated with subsequent division of the external sphincter and healing occurred in these patients. Of the three remaining patients: one woman patient with an anterior fistula was treated successfully with an advancement flap; in another the entire anorectal ring was involved with the fistulous process and, because of minimal symptoms, this patient is currently being followed; and one elderly patient was treated with insertion of a Silastic (Dow Corning, Midland, Minnesota, USA) seton for permanent drainage.

Of the 25 patients in whom primary healing occurred, 24 were available for follow-up and assessment of continence. The patients were asked to report any alteration of continence (for gas, liquid stool, solid stool or mucous discharge). Only nine patients (38 per cent) reported no detectable change in continence. Problems controlling flatus were noted in eight patients (33 per cent). Mucous discharge was noted in six

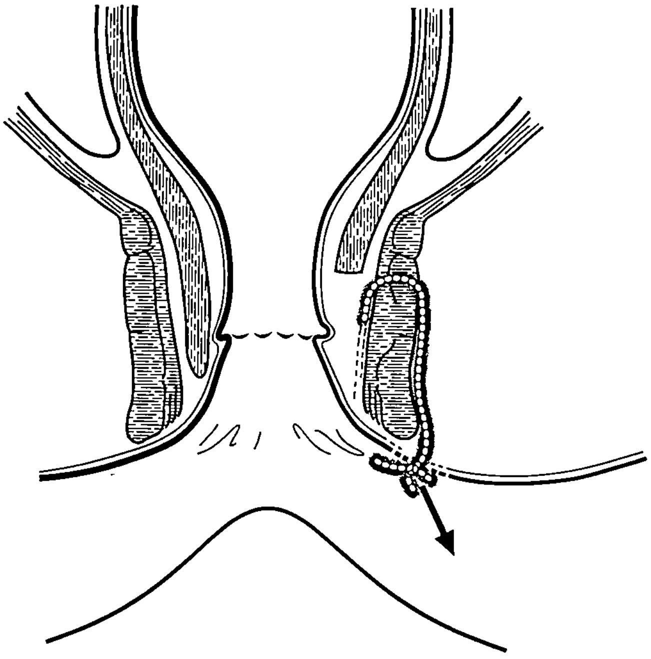

Figure 4 *Removal of seton*

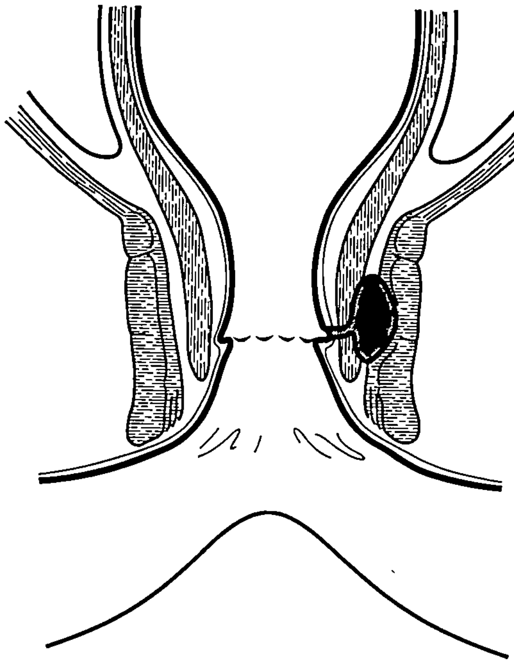

Figure 5 *The originating lesion, an intermuscular abscess*

patients (25 per cent), occurring occasionally in five patients and frequently in one patient. One patient complained of occasional incontinence for liquid stool. This was associated with rectal urgency and irritable bowel syndrome. No patient experienced problems controlling solid stool and none required the use of a protective pad. No patient has required surgical therapy for incontinence.

Discussion

The goals in treating anal fistulae are to cure the fistula and preserve continence. Fortunately, most fistulae are simple, and the 'lay open' technique generally accomplishes these objectives. As the fistula becomes more complex and involves more of the sphincter mechanism correction of the fistula will, by necessity, be associated with increasing alterations in continence The challenge is to minimize this effect.

One of the most significant factors maintaining continence is the anatomical integrity of the sphincter mechanism. Historically, emphasis has been placed on maintaining the anorectal ring (puborectalis) and some maintain that if this muscle remains intact the remaining sphincter can be divided without 'incontinence'[4,5]. Although gross faecal continence can usually be maintained by preserving the puborectalis, preservation of additional amounts of external sphincter will probably have a beneficial effect on function There is no component of the puborectalis in the anterior midline and this probably accounts for the anal manometric findings of high pressures posteriorly in the proximal anal canal compared with high pressures anteriorly in the distal anal canal[6]. This finding supports the belief that division of the sphincter mechanism anteriorly will probably have a greater impact on continence than division of the posterior sphincter mechanism.

Belliveau studied the effects of sphincter division on anal pressure and observed that procedures which maintain anatomical integrity of the external sphincter were associated with higher resting pressure and voluntary squeeze pressure than procedures where the external sphincter was partially divided. The patients in whom the external sphincter was preserved had better functional results[7].

The importance of the anal glands in the pathogenesis of anal fistulae has been stressed[8–11]. These glands in the intermuscular space provide an apparent mechanism for the originating lesion, i.e. an intermuscular abscess (*Figure 5*). The abscess penetrates the external sphincter to enter the ischiorectal space anteriorly or laterally or the deep postanal space posteriorly. Although a true abscess in the intermuscular space is frequently not found at the time of definitive fistula surgery, scarring and evidence of previous infection and/or inflammation is amost always identified.

Table 1 *Functional results*

	St. Mark's Hospital* (%)
Incontinent of flatus	25
Incontinent of liquid stool	17
Incontinent of solid stool	3
Mucous discharge	31
Requires pad	9

* Marks and Ritchie[5], $n = 204$

In his original description Parks described an internal sphincterectomy as well as partial division of the external sphincter. The internal sphincterectomy was used to treat the 'originating lesion', i.e. the infected anal glands and chronic intermuscular infection. Our technique differs in that we perform an internal sphincterotomy and do not divide any of the external sphincter mechanism. We advocate opening the side tracts outside the external sphincter to provide a mechanism of drainage so that healing by secondary intention can take place. The seton is placed around the external sphincter both to promote fibrosis and to assure adequate drainage.

We obtained complete healing in 66 per cent of the patients with posterior fistulae and 88 per cent of the patients with anterior fistulae. The reason the technique is more effective for anterior fistulae is not known but may be related to the deep postanal space. Parks[1] achieved primary healing in 50 patients (63 per cent). Thomson *et al.*[12], using a similar technique, achieved primary healing in 45 per cent of patients. These authors did not stratify their patients as to the location of the fistulae, i.e anterior or posterior, but their results are very similar to the results we obtained by applying this technique to posterior fistulae.

The transanal advancement flap has been used extensively in the treatment of postpartum rectovaginal fistulae and has been applied to cryptoglandular fistulae. Jones *et al.* used this technique to treat 39 patients with a variety of complex fistulae; in six patients these were cryptoglandular in origin unassociated with Crohn's disease and successful healing occurred in all[13]. Wedell *et al.* utilized this technique to treat 27 patients with cryptoglandular fistulae, all of whom were apparently cured[14]. Neither of these studies reported the results based on the location of the fistula, i.e. anterior or posterior This technique was successfully used in one of our patients with a persistent anterior fistula. Although the advancement flap is effective it is not a procedure likely to be in the armamentarium of most practising general surgeons. Our technique, however, can be utilized by any surgeon who has a basic knowledge of anorectal anatomy

Parks and Stitz noted that 17 per cent of patients treated by placement of a seton with subsequent simple removal had partial loss of continence compared with 39 per cent of those who ultimately had division of the seton enclosed muscle[1]. Marks and Ritchie assessed the functional results in 204 patients with potentially high fistulae treated by partial sphincter division and their data and the functional results are presented in *Table 1*.

Our study confirms the findings of the late Sir Allan Parks; this technique can be utilized with success and allows preservation of sphincter muscle. Our data suggest that there is a significant difference in the success rate with regard to anterior and posterior fistulae. Finally, this procedure does not preclude further surgery should primary healing not occur.

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Announcement

European Surgical Fellowships 1990

In February 1990 the Council of The British Journal of Surgery advertised two European Fellowships, each for up to £3000, designed to allow the successful candidates to visit surgical centres of their choice within the European Community. The purpose of this new initiative was to strengthen surgical ties between Britain and the other members of the Community. Applicants were required to hold an FRCS diploma and to be working in surgical practice, whether clinical or research, within the British Isles.

We were pleased to receive seven first-class applications. The task of selecting the winners was made a little easier by the unanimous agreement of Council Members to increase the sum of money available for this inaugural venture. Council has now awarded 1990 European Surgical Fellowships to the following surgeons:

Mr Ashley Dennison MD FRCS (Sheffield)
Mr Colin D. Johnson MChir FRCS (Southampton)
Mr A. Ross Naylor FRCS (Edinburgh)
Mr R. Graeme Wilson FRCS (Edinburgh)

It is Council's intention to offer two European Fellowships for 1991, and a notice to this effect is planned for the November or December issue of the Journal.

R. C. N Williamson
Company Secretary

Br. J. Surg. 1990, Vol. 77, August, 902–906

Evaluation of herniography in the diagnosis of an occult abdominal wall hernia in symptomatic adults

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Outpatient herniography as a means of confirming or refuting the presence of an occult abdominal wall hernia was performed in 50 symptomatic patients, including 13 who had previously undergone hernia repair. Altogether 30 occult hernias were detected in 27 patients, only one of which was considered to be unrelated to the presenting symptoms. On the basis of herniography, 17 patients were spared surgical exploration and, of these 17, 16 obtained a good result. One further patient with a clinically apparent hernia on one side but with contralateral symptoms was spared unnecessary surgery because the contralateral side was radiologically normal. There was one false negative and no false positive examinations. There were three minor complications: two cases of sigmoid colon puncture and one of abdominal wall haemorrhage (all managed conservatively). There were two technical failures. These results support the Scandinavian experience that herniography has a useful role in the management of patients who may have occult hernias as the underlying cause of abdominal wall symptoms.

Keywords: Hernia, herniography

Hernias were recognized as long ago as 1500 B.C. by the Egyptians and hernia surgery was documented by Celsus in A.D. 25[1]. However, hernias remain an important surgical challenge. Given that inguinal hernias occur in approximately 0·1 per cent of the adult population[2], there is a large economic and logistic consideration.

Occasionally the diagnosis of hernia may not be clear, particularly in the patient with a painful hernia repair without a clinically detectable recurrence. In such uncertain situations the treatment of groin pain is often by trial and error, frequently resulting in exploration of the groin. Herniography is a technique which might potentially reduce the number of unhelpful surgical explorations It is a simple, radiological, outpatient procedure which has received scanty attention outside Scandinavia[3].

In this report herniography is described along with the results obtained in adults with symptoms but not signs of hernia

Patients and methods

Herniographs were performed in 50 patients between August 1987 and April 1989. One patient had two herniographs Any patient over 18 years of age who had symptoms of pain or a history of a lump suggesting an abdominal wall hernia, which could not be demonstrated clinically, was asked to participate in the study. There were two main groups of patients· firstly, those who had a history of groin pain or of a lump (or both) who had not undergone previous surgery ($n=37$), and secondly, patients with symptoms either ipsilateral or contralateral to a previous hernia repair ($n=13$) All patients were followed up for a median of 14 months (minimum 6 months).

All patients gave informed consent and the technique used was adapted from that described by Ekberg[3]. All examinations were performed without sedation in outpatients by one consultant radiologist (J.W.). After voiding the patient lay supine on a tilting fluoroscopy table. The site for abdominal wall puncture was infiltrated with 1 per cent lignocaine Initially, the examination was performed as originally described[3] by inserting a needle laterally in the left iliac fossa at the lateral border of the rectus muscle ($n=27$), after two inadvertent punctures of the sigmoid colon the site was changed to the midline just below the umbilicus ($n=24$) No complications occurred using the latter site

A 20 French gauge lumbar puncture needle was introduced into the peritoneal cavity and a small amount of contrast injected and screened to ensure that the needle was lying free within the abdomen. A non-ionic low osmolar contrast medium (50 ml of either Iopromide (Schering, Burgess Hill, UK) or Iopamidol (Merck, Alton, UK) containing 300 mg iodine/ml was then injected. The needle was withdrawn and the patient turned prone and then semi-erect and erect to allow the contrast to flow into the area under study The patient was asked to cough and then to perform a Valsalva manoeuvre. Anteroposterior and 45° oblique views were exposed In the case of an unusual site, the symptomatic area was first marked on the skin using a metal indicator, which enabled this site to be related to any abnormal radiological anatomy. In radiologically uncertain areas, video recordings were made for subsequent evaluation by the radiologist and senior clinician. *Figure 1* is a diagram of those features which can be demonstrated by herniography. The medial umbilical ligament, representing the urachal remnant, divides the diagram into left and right sides The lateral umbilical fold, raised by the inferior epigastric vessels, divides the inguinal region into the lateral inguinal fossa (where indirect inguinal hernias arise) and the medial inguinal fossa The latter is demarcated by the medial umbilical fold, representing the obliterated umbilical veins, from the supravesical fossa. Direct inguinal hernias may arise from either the medial inguinal fossa or the supravesical fossa. The lateral umbilical fold is sometimes indistinct, but may be seen in 47 per cent of patients[4]. Occasionally this makes the differentiation of direct from indirect hernias difficult.

Results

Group 1

This consisted of 37 patients who presented with lower abdominal pain and who had not undergone previous hernia repair. These patients could be further subdivided into four groups· (a) 23 patients with unilateral groin pain ($n=20$) or right iliac fossa pain ($n=3$) and no history of a lump; (b) eight patients with unilateral groin pain ($n=5$) or left iliac fossa pain ($n=3$) and a history of a lump; (c) two patients with bilateral groin pain but no lump; (d) four patients with a hernia on one side but additional groin symptoms on the other side.

Group 1a. Sixteen of these 23 patients had a normal herniograph. Of these 16 patients, three with right iliac fossa

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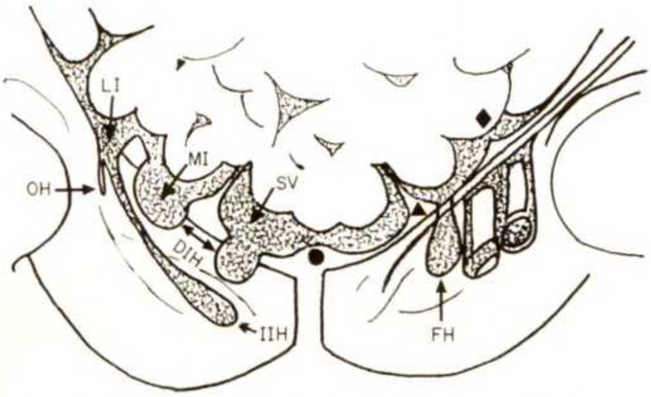

Figure 1 *Schematic diagram of a herniograph:* ●, *medial umbilical ligament;* ▲, *medial umbilical fold;* ◆, *lateral umbilical fold; SV, supravesical fossa; MI, medial inguinal fossa; LI, lateral inguinal fossa; OH, obturator hernia; IIH, indirect inguinal hernia; DIH, direct inguinal hernia; FH, femoral hernia*

pain had previously undergone extensive radiological investigation. Early in the series two of these three were explored. One had normal anatomy and the other had a small direct inguinal hernia (the only false negative in the series). In retrospect, this latter patient would now be considered to have a small radiological hernia. One patient had repeat herniography; the first examination suggested a possible direct inguinal hernia but video herniography performed 4 months later was considered to be normal. Three patients with continuing symptoms had a very good response to bupivacaine injection at the site of pain and were therefore considered to have a nerve entrapment syndrome. Only one of the 16 patients with a normal herniograph has not improved or become asymptomatic. This patient has previously had surgery for Crohn's disease and does not warrant further operation on clinical grounds.

Seven of the 23 patients with unilateral groin pain had an abnormal herniograph. Four of these seven patients had an inguinal hernia on the symptomatic side and one further patient had bilateral inguinal hernias (*Figure 2*). A sixth patient (female) had a right obturator hernia (*Figure 3*). This woman had had right groin pain associated with some anterior thigh pain for 2 years. All seven hernias in these six patients were confirmed at surgery and their repair markedly improved or resolved the symptoms. The remaining patient (female) had *right*-sided groin symptoms and a *left* obturator hernia. Some improvement in symptoms has occurred on follow-up without surgery.

Group 1b. Eight patients with a history of a lump were all found to have pathology. Three of them had inguinal hernias on herniography and this was confirmed at surgery. Two had a processus vaginalis. One was a woman and the other a man whose intermittent 'lump' turned out to be an undescended testis lying at the external ring; both had surgery with a good outcome. One patient was found to have an interstitial hernia which, despite impressive herniographs, was never clinically apparent (*Figure 4*). This patient had an intermittent swelling in the left iliac fossa which she first noticed after lifting a heavy bag. She was moderately obese and repeated clinical examination failed to reveal a hernia. The final two patients had unusually sited lumps in the left iliac fossa. One of them, with a lump underlying the lateral border of the left rectus muscle, had a normal herniograph. At operation an intramuscular lipoma was found. The herniograph was considered valuable insofar as unnecessary dissection was avoided. Herniography was unsuccessful in the other patient because of multiple adhesions after anterior resection for rectal carcinoma 30 months previously. Exploration in this patient, who was grossly obese, revealed a metastatic tumour deposit in the anterior rectus sheath.

Group 1c. Two patients presented with bilateral groin pain. A bilaterally patent processus vaginalis was demonstrated by herniography in one. Initially there was no operation but persistent symptoms resulted in surgical exploration 6 months later. The radiological findings were confirmed and following surgery he became asymptomatic. The second patient had no radiological hernias despite convincing symptomatology. She subsequently had psychiatric treatment and her symptoms improved.

Group 1d. Four patients had clinical hernias on one side but symptoms on the opposite side. Two of these patients also reported a contralateral lump which was not obvious in the outpatient department but which was confirmed radiologically and surgically in both cases. A third patient had a definite hernia on the right but a lump on the left which clinically felt like enlarged lymph nodes. Herniography demonstrated bilateral indirect inguinal hernias and at operation these bilateral hernias were repaired, but lymph node enlargement was verified on the left and biopsy revealed Hodgkin's lymphoma. The fourth patient had a hernia on one side but a normal herniograph for the opposite site. Following repair of the hernia the contralateral symptoms disappeared.

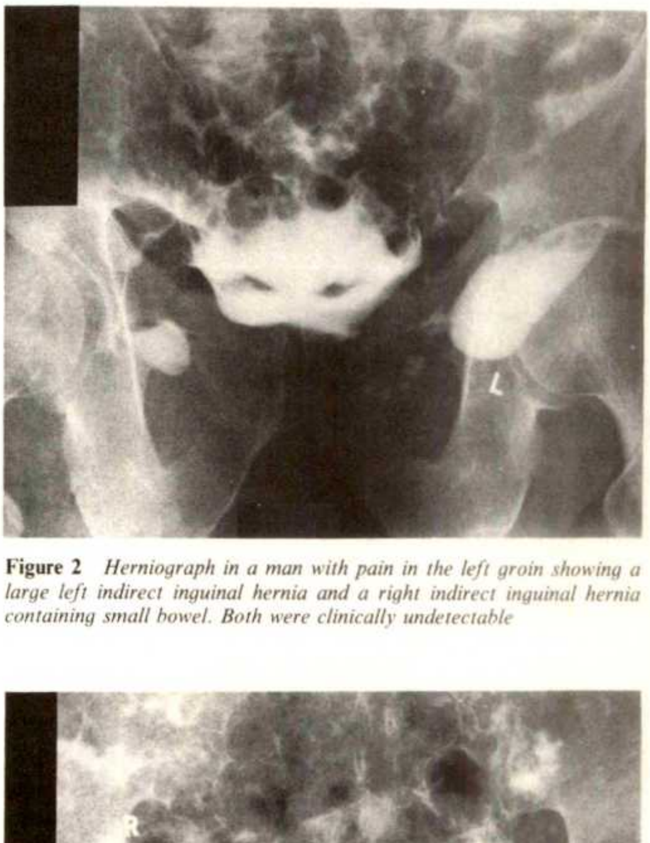

Figure 2 *Herniograph in a man with pain in the left groin showing a large left indirect inguinal hernia and a right indirect inguinal hernia containing small bowel. Both were clinically undetectable*

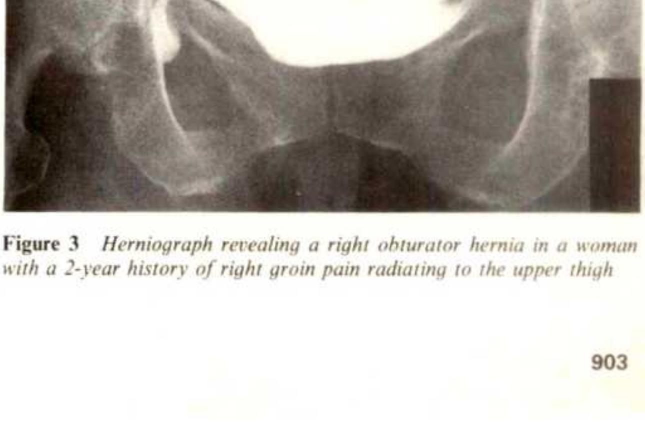

Figure 3 *Herniograph revealing a right obturator hernia in a woman with a 2-year history of right groin pain radiating to the upper thigh*

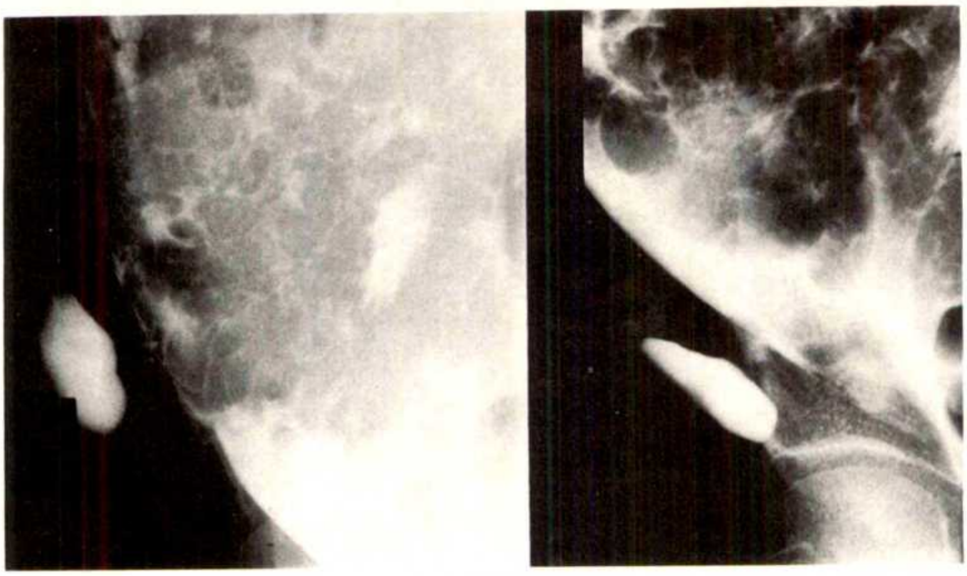

Figure 4 *Herniograph demonstrating an interstitial abdominal wall hernia in a woman who had noticed a lump in the left iliac fossa*

Group 2

There were 13 patients in this group. Of five patients who had undergone bilateral herniography, four had unilateral symptoms with recurrent herniation detected radiologically and confirmed at operation at the site of pain; in fact, one of these had bilateral recurrences. The fifth patient had a radiologically detected recurrence on the side contralateral to his symptoms; this was repaired and his symptoms completely settled.

Of eight patients who had had unilateral repair, two had symptoms on the side opposite to the previous hernia surgery and six were symptomatic in the previously operated side. One of the two patients with contralateral symptoms had a hernia at the site of the pain which was confirmed at operation. The other had a failed examination due to a vasovagal episode precipitated by occult haemorrhage from an inadvertent puncture of the inferior epigastric vessels. He underwent exploration of the symptomatic groin and a small indirect inguinal hernia was repaired. Of the remaining six patients, two had corresponding hernias confirmed on herniography and, at surgery, two had a contralateral recurrence and two had no demonstrable pathology. One of these was explored surgically early in the series and no recurrence was found. The other has been treated with short wave diathermy and ultrasonic therapy to the scar, with complete resolution of symptoms.

Morbidity

Three (6 per cent) of the 51 herniographs performed were associated with a complication. Two of these were inadvertent puncture of the sigmoid colon. One patient had no ill-effects. The second presented 8 h after the examination with left iliac fossa pain and local peritonism with no constitutional upset. His condition settled after 24 h treatment with intravenous fluids and antibiotics (cefuroxime 750 mg t.d.s. and metronidazole 500 mg t.d.s.). Since these two episodes, the site of puncture has been altered as detailed above. The third patient suffered a haemorrhage due to inadvertent puncture of the inferior epigastric vessels. The patient had a vasovagal attack and the procedure was abandoned. After an observation period of 6 h he was allowed home.

Overall results

The overall results are summarized in *Figure 5*. Herniography detected 'occult' hernias in 27 patients: 20 with unilateral inguinal hernias, two with bilateral occult inguinal hernias, three with patent processus vaginalis (bilateral in one), and two with obturator hernias. Only in one patient with a left obturator hernia was the hernia considered to be unrelated to the presenting symptoms.

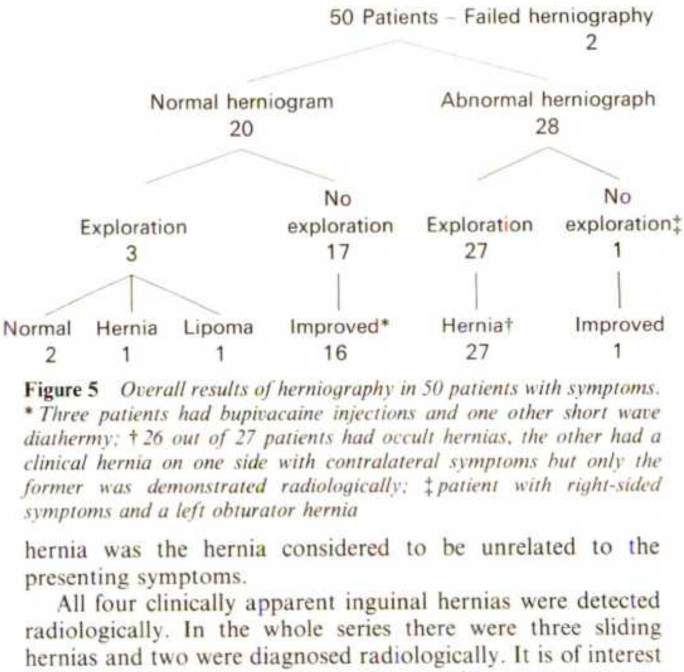

Figure 5 *Overall results of herniography in 50 patients with symptoms. * Three patients had bupivacaine injections and one other short wave diathermy; † 26 out of 27 patients had occult hernias, the other had a clinical hernia on one side with contralateral symptoms but only the former was demonstrated radiologically; ‡ patient with right-sided symptoms and a left obturator hernia*

All four clinically apparent inguinal hernias were detected radiologically. In the whole series there were three sliding hernias and two were diagnosed radiologically. It is of interest that a hernia contralateral to that causing symptoms was demonstrated in four of 13 patients who had been previously operated upon. All patients who had surgery became asymptomatic.

On the basis of herniography a total of 17 patients were spared exploration, although three had local anaesthetic infiltrations and one had short wave diathermy. All but one patient (who had Crohn's disease) have become asymptomatic or markedly improved. An additional patient with a clinical hernia on one side but symptoms on the contralateral side was spared surgery on that side because herniography revealed only the clinically apparent hernia. This patient also became asymptomatic following surgery.

There were no femoral hernias detected radiologically, although this diagnosis was suggested clinically in one case. However, an indirect inguinal hernia was found radiologically and surgically confirmed.

Discussion

Herniography was first reported in Canada in 1967[5] when it was used to detect contralateral hernias in children. In a series of 562 children with a clinically obvious hernia, 23 per cent were found to have a significant contralateral hernia[6] This finding led Kiesewetter and Oh to conclude that herniography should be a routine examination in infants[7]. Rowe *et al.*[8], however, demonstrated that patency of the processus vaginalis decreases from 63 per cent at 2 months of age to 41 per cent at 2 years of age and that this frequency is maintained to the age of 16 years. Moreover, only about half of those with a unilateral hernia and a patent processus on the opposite side go on to develop a contralateral hernia[8]. Observations such as these make the significance of a radiologically detected abnormality in children difficult to interpret. Whilst herniography may occasionally prove useful, it does not appear to be indicated routinely in children with hernias.

However, the present study confirms the results from Scandinavia, that herniography has an important role to play in adults presenting with clinically uncertain groin symptoms. Pain in the groin after hernia surgery may be due to recurrence, but it may also be due to postoperative nerve entrapment, osteitis of the pubic tubercle or, indeed, conditions unrelated to the previous surgery[9]. Postoperative scarring of tissues and disturbance of normal anatomy make clinical diagnosis difficult. The anatomical derangement resulting from herniography and recurrent hernias, however, is easily seen on herniography, usually having the same appearance as those in virgin groins except that the hernia neck is often more distinct[3]. In a series of 106 patients who had pain or bulging at the site of a previous inguinal hernia repair, 80 per cent of those with a bulge had hernias radiographically and 42 per cent of those with pain had a hernia[10] Of the 12 successful herniographs performed in our patients with a previous hernia repair, two were normal and only six patients had a recurrent hernia on the same side as the presenting symptoms (one was even bilateral). In four patients the recurrence was, surprisingly, on the contralateral side, yet symptoms resolved following radiologically-directed repair.

The majority of herniographs in this series and in the larger series in the literature were performed to evaluate obscure pain in non-operated groins. In the present series.there were 37 such patients with 30 hernias detected in 27 (including three patients with a patent processus vaginalis). Equally important, exploration was avoided in 17 patients with a normal herniograph and unnecessary bilateral groin exploration was avoided in a patient with bilateral symptoms but a hernia only on one side. All patients with a reliable history of a lump had pathology Radiographic examination of 501 patients, for pain compatible with a hernia but with a normal or inconclusive physical examination, revealed an overall frequency of hernias in 51 per cent and in 36 per cent of those with a completely normal physical examination[11]. In a study of 78 male athletes, predominantly soccer players, with 101 painful groins, radiological hernias were found in 84 per cent[12]. The herniograph also suggested an alternative diagnosis in some of the other patients, such as osteochondritis of the pubic symphysis, avulsion fracture at the origin of the adductor muscles and osteoarthritis of the hip joint[12] Apart from musculoskeletal disorders, the other common obscure groin pain is urogenital in origin, in particular prostatitis[13]. While herniography cannot diagnose urological disorders, its converse application has been suggested to exclude a hernia as a cause of longstanding problems presumed to be urological in nature[14]

There is no place for herniography in patients with an established clinical hernia. In the present series all clinical hernias were demonstrated in the course of examining the contralateral symptomatic groin and no extra information was gained. A study from Lund, performed on the assumption that herniography would reveal additional herniation on the same side and decrease overlooked concomitant hernias, was equally disappointing. Although a number of contralateral asymptomatic occult hernias were discovered radiographically, in no instance in 88 patients did the herniograph alter management of the apparent hernia[15]

The management of adult patients with a radiologically patent processus vaginalis is not immediately apparent. This study discovered four cases of patent processus vaginalis in three patients. In two there was a history of a lump so that the decision to operate was made easily. In the third patient the radiographic findings did not convincingly explain the symptoms, but when the pain failed to settle with time, surgery was performed with symptomatic improvement. However, the frequency of patent processus vaginalis is around 15–30 per cent in post-mortem studies, and the indirect inguinal hernia rate is less than 5 per cent[8]. The finding of a patent processus vaginalis on herniography must, therefore, be considered carefully before embarking on surgery. While herniography may demonstrate an abnormality, that abnormality need not necessarily be the cause of symptoms.

Similarly, the finding of an obturator hernia must be considered in the light of symptoms and the possibility of strangulation The present series contained two obturator hernias, one of which seemed clinically to be causing symptoms and was operated on. Some authors feel that even small obturator hernias should be repaired electively to avoid the morbidity and even mortality of strangulation[3,16]. In contrast, Perrsson *et al.* reported the course of 15 patients diagnosed by herniography as having an obturator hernia and concluded that surgery was rarely required[17]. Devlin[2] has indicated that the danger of strangulation is predominantly in women with a right-sided obturator hernia

There were no femoral hernias detected radiologically in this series. This may be because femoral hernias do not pose the same diagnostic problem as inguinal hernias, but it is interesting that some studies have employed femoral phlebography to demonstrate femoral hernias[18], a technique not used here.

The complication rate of herniography has been reported as 5·8 per cent, with contrast medium being inadvertently instilled into the rectus muscle, mesentery, bowel, bladder and vessels, with abdominal wall cellulitis, haematoma formation, or even peritonitis resulting[19,20]. This small series had a complication rate of 6 per cent and, by modifying the technique as described, it may be possible to reduce this.

In summary, herniography is a technique used extensively in Scandinavia[3] and sporadically in other countries[15]. It cannot only alter clinical management but it can also be done with a low morbidity and technical failure rate Groin pain in the adult is a condition which may tempt the surgeon to explore blindly with no guarantee of success. Herniography is a useful technique which helps to rationalize the treatment of these difficult problems in both non-operated and previously operated groins. However, it adds no further information in cases of clinically obvious hernia.

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Case report

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Interstitial hernia: a report of four cases in infants

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Interstitial hernias are uncommon and may present in adults and children. The first successful surgical repair in an adult was performed by Sir Astley Cooper in 1812[1] and Goyrand[2] coined the term 'inguino-interstitial' to describe a hernial sac passing between the layers of the abdominal wall. Hernias occur more frequently in the right groin and the association with an undescended testis is well recognized[2,3]. We report four cases in young children.

Case report

Four infants, three boys and one girl, presented between the ages of 4 weeks and 16 months. Each mother reported the finding of an intermittent swelling in the right groin and on examination this was found to be lateral to and above the internal inguinal ring The edge of the swelling was poorly defined, being deep to the external oblique muscle. In the three boys the swelling was tender and not fully reducible and associated with an ipsilateral impalpable testis. In the girl there was a contralateral indirect inguinal hernia and a previous anoplasty for an ectopic anus (*Table 1*)

Operative findings and procedure

Operations were performed through a skin crease incision in the right groin and the external oblique aponeurosis opened to expose the hernial sac In all cases, the neck of the hernia was at the internal inguinal ring and the hernial sac lay between the external and internal oblique muscles. In cases 1 and 2, a rudimentary gubernaculum was identified between the muscle layers and there was no opening at the site of the external inguinal ring. In case 3, the gubernaculum passed through the open external ring to an ectopic position lateral to the neck of the scrotum. In cases 1, 2 and 3 the ipsilateral testis was adjacent to the hernial sac, laying between the oblique muscles In case 4, the fundus of the hernial sac was adherent to the deep surface of the external oblique aponeurosis, with no extension through the open external ring.

A herniotomy was performed in each case, ligating the neck of the sac at the internal inguinal ring. In cases 1, 2 and 3, the testis and spermatic cord were mobilized and the testis placed in a subcutaneous pouch low in the scrotum. In cases 1 and 2, the external inguinal ring had to be opened by sharp dissection.

The wound was closed with absorbable sutures to the external oblique aponeurosis, Scarpa's fascia and the subcuticular tissues

Results

In case 1, the testis was noted to be atrophic 6 months after operation. Cases 2, 3 and 4 made an uneventful recovery, case 4 also having a left inguinal herniotomy performed under the same anaesthetic.

Discussion

Interstitial hernias are sited between the layers of the abdominal wall but their neck may not be at the internal inguinal ring since they may present through the Spigelian fascia[4]. They may be bilocular, being in continuity with an inguinal or femoral hernia[2]. Twenty per cent are properitoneal, lying between the peritoneum and the transversalis fascia; 60 per cent are intermuscular between the internal and external oblique muscle and 20 per cent are superficial, lying between Scarpa's fascia and the external oblique muscle[5]. The terms, 'interstitial' and 'interparietal' are synonymous although Barling[6] reserves 'interstitial' for intermuscular hernial sacs, as in these four cases.

Langton[3] reviewed 50 000 patients with hernias in whom 42 were interstitial (0 08 per cent) and 19 of these presented in the first year of life. A male preponderance has been consistently reported and in two-thirds of males, interstial hernias are associated with abnormalities of testicular descent[2,3,6,7], reflecting an abnormality of descent of the processus vaginalis[8].

The aetiology in cases 1 and 2 may be related to the absence of the external inguinal ring; this rare anomaly has been described in a newborn with bilateral interstitial hernias associated with undescended testes[9]. In case 3, the gubernaculum

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Table 1 *Clinical features of four infants with an interstitial hernia*

Case	Age at presentation	Age at operation	Sex	Birth weight (kg)	Side	Associated features
1	4 weeks	4 months	M	3·6	R	Impalpable testis
2	5 weeks	5 weeks	M	3·2	R	Impalpable testis
3	3 months	3 months	M	3·0	R	Impalpable testis
4	16 months	20 months	F	3·0	R	Ectopic anus, Left indirect inguinal hernia

R, right

passed through an open external ring to the lateral aspect of the scrotal neck but the testis and hernial sac failed to follow the path of the gubernaculum. In the girl, case 4, the hernial sac was tethered by adhesions to the deep surface of the external oblique muscle.

In contrast to inguinoscrotal hernias, interstitial hernias present with an ill-defined swelling lying above the inguinal ligament and extending upwards and laterally from the internal inguinal ring. The swelling may be irreducible as incarceration is a common mode of presentation[6] and is difficult to distinguish from a torsion of the undescended testis. In many instances, the true nature of the hernia is only apparent at operation. Cases 2 and 3 presented with a painful, irreducible swelling but the site and contents of the hernia were not easily defined on examination because of the overlying external oblique muscle. The risk of strangulation and vascular accident to the testis demanded early operative treatment. Postoperative testicular atrophy, as in case 1, is well recognized following infant hernitomy[10] and is more common when there has been an associated undescended testis.

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Penetrating visceral injuries of the neck: results of a conservative management policy

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A study of the conservative treatment of 109 patients with penetrating neck injuries was carried out over 3 years. Patients with clinical or radiological evidence of injury to the oesophagus or trachea were included in the study while nine patients with major vascular trauma were explored immediately and excluded. Three late vascular operations were performed. The remaining 106 patients were treated conservatively. There were two deaths, both from associated injuries. The remaining 104 patients were treated successfully with only three cases of minor wound sepsis. We conclude that oesophageal and tracheal injuries after stab injuries and low velocity gunshot wounds can be treated successfully by non-operative treatment.

Keywords: Penetrating neck injuries, trachea, oesophagus, trauma

The management of penetrating injuries of the neck is controversial. Whilst all authors are in agreement that major vascular injuries require exploration, some advocate mandatory exploration for all wounds that penetrate the platysma[1–4] while others favour a selective approach, exploring only those patients with symptoms, signs, or investigative evidence of injury to the trachea or oesophagus[5–11]. Proponents of the mandatory approach argue that clinical and radiological assessment are unreliable and that major, potentially fatal, injuries may be missed. Those employing the selective policy cite the high incidence of negative explorations with its attendant morbidity rate if routine exploration is employed. A prospective study performed at this institution justifies the selective approach adopted by this department[11].

The present study was undertaken because of two observations that arose while employing this policy. Firstly, we observed that several of our oesophageal repairs broke down, resulting in fistulae and prolonged hospital stays. Secondly, a number of patients with clinical and radiological evidence of visceral injury refused operation but incurred no untoward complicatons following conservative management. This study evaluates the role of conservative management of penetrating wounds of the neck in patients with suspected or proven injury to the trachea or oesophagus.

Patients and methods

The study was carried out prospectively from July 1984 to December 1987 in one of the six surgical units at King Edward VIII Hospital, Durban. Only patients with injuries between the clavicles and mandible were considered and nine patients with evidence of a major vascular injury were excluded. In all, 109 patients were reviewed. There were 95 males and 14 females with an age range of 12–60 years (mean 29 6 years) Wounds resulted from stabbing with a knife (90 patients), gunshot (12 patients) or other implement (seven patients).

Wounds were cleansed with an antiseptic solution (Eusol, 0·3 per cent sodium hypochloride) and left open, if already sutured, stitches were removed to allow free drainage and to avoid any accumulation in the tissues should a leak occur A dry dressing was applied. The wounds were not debrided and missile fragments were not removed

Diagnosis of significant injury was made by clinical examination and radiological investigation. Symptoms of dysphagia, haematemesis, haemoptysis and hoarseness, and signs of subcutaneous emphysema or blowing wounds, were specifically sought. Chest radiographs with biplanar neck views were obtained. All patients with gunshot wounds underwent a contrast swallow (Dianosil®, Glaxo (Pty) Ltd , Germiston, South Africa) examination. This particular contrast was used because it is water soluble and is readily absorbed from the tissues; hence repeat contrast swallow can be done without the presence of previously leaked contrast in the tissues. Patients with stab wounds of the neck were divided into two groups on the basis of the response to swallowing a mouthful of water Those who experienced severe pain on swallowing underwent a contrast swallow examination whilst those without severe discomfort had no further investigation The presence of retropharyngeal air on plain radiography was not an indication for further investigation.

All patients were given nothing by mouth and had intravenous fluids administered They received one dose of tetanus toxoid vaccine (tetanus vaccine BP, Wellcome (Pty) Ltd , Kempton Park, South Africa) and 4 ml Bicillin® (Wyeth Laboratories (Pty) Ltd , Isando, South Africa) on admission Those with severe pain or discomfort were given in addition a full course of intravenous antibiotics (cloxacillin 4 g/24 h, metronidazole 1 5 g/24 h)

Patients whose contrast study demonstrated a leak were given nothing by mouth until a repeat contrast swallow showed no further leakage. The rest of the patients were kept nil by mouth for 24–48 h.

Results

In only 44 patients (40 per cent) were symptoms and signs of suspected visceral injury elicited (*Table 1*), dysphagia and subcutaneous emphysema being the most common findings Biplanar radiographs revealed prevertebral air in 22 patients (20 per cent) Fifteen patients had pneumothorax on chest radiography, eight of which required intercostal drainage. A further 13 patients were shown to have haemopneumothorax due to separate chest wounds.

A total of 29 contrast swallows were performed, 25 of which were negative. Of the four positive results, two were associated with stab wounds and two with gunshot wounds. None of these positive swallows showed gross leakage of contrast material and operative repair was not performed (*Figure 1*). Repeat contrast examination on day 5 showed no leakage, demonstrating that the leak had sealed spontaneously without complication. The other 25 patients recovered uneventfully. Of

Table 1 *Main clinical features in 109 penetrating wounds of the neck*

Clinical feature	No of patients
Nil	65
Dysphagia	24
Subcutaneous emphysema	17
Haematoma	6
Hoarseness	4
Brown-Séquard syndrome	2
Brachial plexus lesion	2
Haemoptysis	1
Cerebrospinal fluid leak	1
Chylous leak	1

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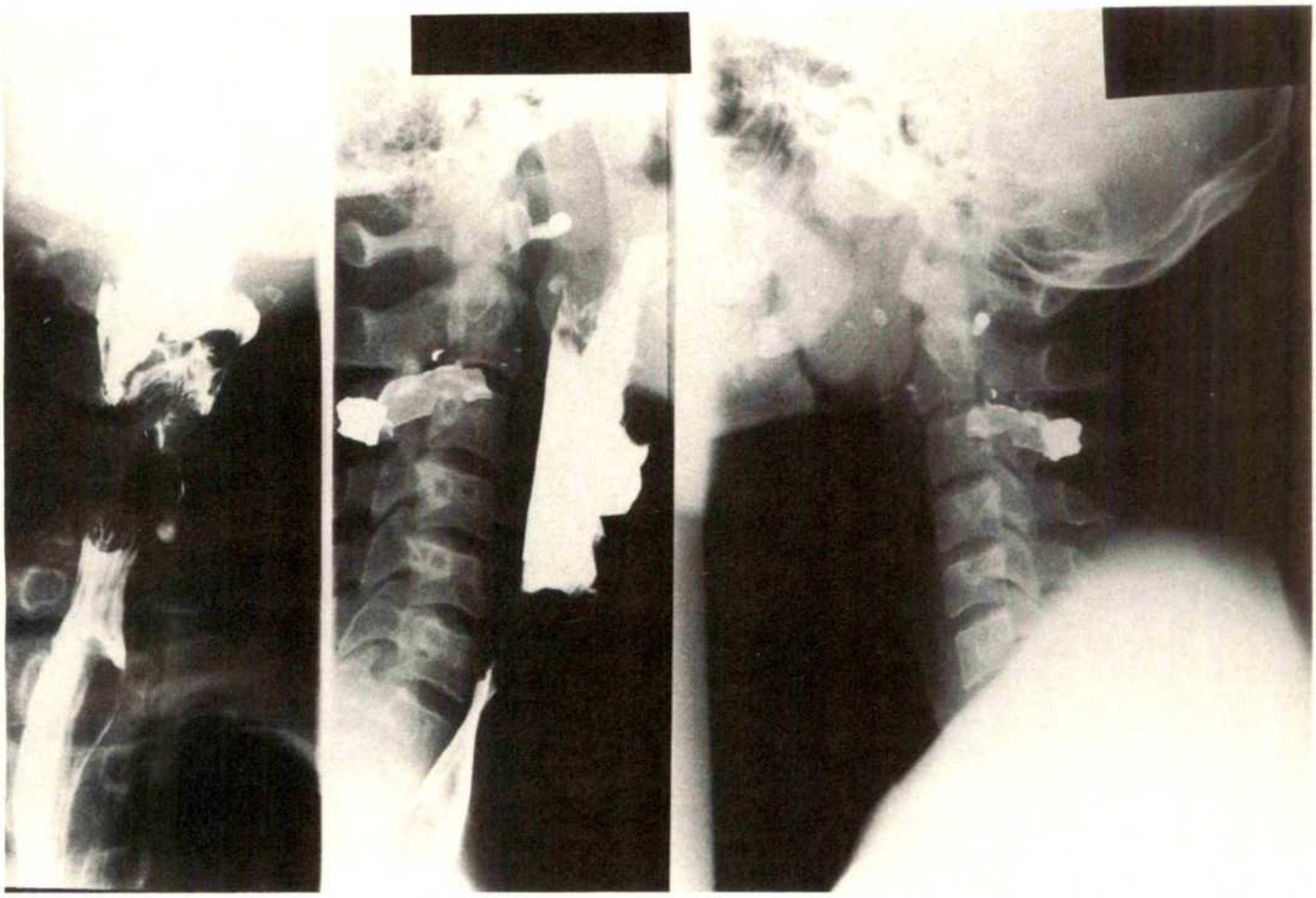
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Figure 1 *Dionosil swallow demonstrating oesophageal injury with minimal leakage of contrast material. The fragmented missile is seen in the neck*

the remaining 80 patients who were excluded from further investigation by virtue of no symptoms on water swallowing, none developed major complications related to the oesophagus or trachea. Five arch angiograms were performed, for expanding neck haematomas. Three of these revealed vascular injury. These three patients were the only ones who underwent operative intervention, 4, 23 and 72 h after admission.

Injury to the trachea was inferred from the presence of haemoptysis (one patient) and/or hoarseness (four patients). Subcutaneous emphysema, combined with a negative Dionosil swallow and normal chest radiograph suggested either tracheal or oesophageal injury or both (13 patients). None of the 18 patients fulfilling these criteria required surgery.

There were two deaths in the series. A 12-year-old girl with gunshot wounds of the head and neck died within 2 h of admission from cerebral trauma. The remaining patient died on the fourteenth day from septicaemia associated with 50 per cent burns.

The majority of patients were discharged by the fifth day. Three patients had a delayed discharge because of minor wound sepsis but all left hospital within 8 days of admission. Prolonged admission was necessary only for those patients with associated injuries, one patient with Brown–Séquard syndrome being discharged after 45 days and one patient with head injuries after 134 days.

Discussion

Experience with neck injuries sustained in military conflict suggested a policy of mandatory exploration of all wounds which penetrated the platysma[12,13]. However, the majority of these injuries resulted from high velocity missiles and this approach may not be appropriate to civilian practice where the majority of injuries arise from stab wounds[14]. There is no doubt that high velocity injuries to the neck must be explored, but a selective policy is justified when dealing with stab wounds and may also be applied to low velocity gunshot wounds, although the reported missed injury rate is higher than with knife wounds[13,15] and a higher index of suspicion is required. The use of a mandatory exploration policy results in no missed injuries but this must be weighed against the morbidity rate and cost of negative explorations. Proponents of the mandatory policy claim that hospital stay in those patients undergoing a negative exploration is no greater than those undergoing observation[2,3,10,15] whilst those favouring a selective approach disagree[5].

It is well recognized that isolated injuries of the oesophagus or trachea may present with minimal symptoms and signs[6]. The paucity of clinical signs and the failure to demonstrate any injury after investigation implies that these injuries are minimal. The sensitivities of oesophagography and oesophagoscopy range from 47 to 93 per cent and from 29 to 100 per cent respectively[6,16–18]. If the high false negative rate of these investigations is true and if the missed injury rate quoted by those employing mandatory exploration is also true, then it follows that a number of those patients who recovered fully without surgery must have sustained penetrating injuries of the oesophagus or trachea which sealed spontaneously. From this it must be concluded that not all wounds of the oesophagus or trachea require surgical intervention. Our findings support this observation. Of the 29 patients who merited further investigation on the basis of the water swallowing test only four demonstrated leakage of contrast material. In all cases this was minimal and repeat swallow on day 5 demonstrated that the leak had sealed spontaneously without complication. We would propose that a negative contrast study indicates either no injury or such a minimal injury that surgery is not merited. Although all were treated conservatively regardless of the contrast swallow findings, this investigation was necessary to separate those whose injuries were already sealed from those who still showed a leak, requiring more prolonged conservative management. With regard to tracheal injury, not one of our patients required operative intervention and in the absence of life-threatening airway problems a conservative approach in this group of patients is advocated.

Our results are at variance with the reported mortality rate of missed oesophageal injuries[5,15,19]. This may be explained by our strict regimen of nil orally, intravenous fluid therapy, and parenteral antibiotics.

From this study we conclude that patients with minimal symptoms of visceral injury following penetrating cervical wounds may be selected for further investigation on the basis of a simple water swallowing test. Those with severe pain on swallowing, and all gunshot victims, should be submitted to contrast swallow examinations. Patients with a normal investigation and those with minimal leakage of contrast material may be managed conservatively, the latter group having a repeat examination on day 5. As with other authors, we advocate mandatory exploration for all vascular trauma but we conclude that oesophageal and tracheal injuries are not absolute indications for surgery.

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Peripheral lymph node tuberculosis: a review of 80 cases

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One hundred and ninety-two patients with peripheral lymphadenopathy were screened and 80 patients with tubercular lymphadenitis were studied. Their ages ranged from 1 to 65 years; most were younger than 30 years and there was a slight female preponderance (1·2:1). Seventy per cent of patients were of low socioeconomic status. Of the 80 patients, 56 had affected cervical nodes, seven had inguinal nodes, five had axillary nodes and 12 had multiple sites of lymph node involvement. All had enlarged nodes which were matted in 44 cases and discrete in 18 cases, while the rest had either an abscess or a discharging sinus. Fifty-nine cases (74 per cent) showed a positive Mantoux test and four cases (5 per cent) had associated pulmonary tuberculosis. Fine needle aspiration cytology gave a positive diagnosis in 66 cases (83 per cent). Fifty-two cases showed a positive culture for Mycobacterium tuberculosis *of human type in Lowenstein–Jensen medium. Short-term chemotherapy (9 months) consisting of rifampicin, isoniazid and ethambutol gave an excellent result. Surgery was not required in any of the cases.*

Keywords: Tubercular lymphadenitis, Mantoux test, fine needle aspiration cytology, antitubercular chemotherapy

Tuberculosis is widely prevalent in all age groups and in most countries of Asia and Africa. It ranks high as one of the killers of children in our region of India and causes a major public health problem with enormous sociological and economic implications. The diagnosis and management of peripheral lymph node tuberculosis remains a major problem in such areas owing to illiteracy, ignorance and lack of awareness of the complications of the disease The lack of facilities for investigation and adequate medical treatment, coupled with the poor economic condition of the people, plays a major role in the late presentation of patients with complications.

The present study was carried out to determine the incidence of peripheral lymph node tuberculosis in our area, its clinical presentation and pathological aspects, and to assess the value of short-term chemotherapy.

Patients and methods

The present study involved 80 patients with peripheral lymph node tuberculosis from various parts of Orissa who attended the surgical, paediatric, medicine, and chest and tuberculosis departments of M.K.C.G. Medical College Hospital, Berhampur, Orissa from January 1987 to July 1988. They were drawn from a total of 192 patients presenting with peripheral lymphadenopathy over this period. For the purpose of this study peripheral lymph nodes were taken to include the cervical, axillary and inguinal groups of nodes Other sites such as epitrochlear, popliteal and scaleni nodes were excluded because lesions at these sites are extremely rare

After a detailed history and clinical examination, investigations performed included the erythrocyte sedimentation rate (ESR), haemaglobin concentration, Mantoux test (positive result >10 mm in diameter), sputum examination for acid-fast bacilli, chest radiography, biopsy of enlarged node and culture in Lowenstein–Jensen medium

After confirmation of the diagnosis all patients were given short-term chemotherapy consisting of ethambutol plus isoniazid plus rifampicin for 2 months followed by isoniazid plus rifampicin for 7 months All the drugs were taken orally in a single dose, preferably on an empty stomach. Dosage was determined by the patient's weight (*Table 1*).

Patients were followed at 3-monthly intervals for 9 months and progress was assessed by local and general examination and determination of the ESR and haemoglobin concentration.

Results

Tuberculosis was the commonest cause of peripheral lymphadenopathy, accounting for 43 per cent of such cases in our practice. The total number of patients with peripheral lymph node tuberculosis was 83, of which 80 cases were included in the present study as three patients did not return for follow-up. Other causes of lymphadenopathy were chronic non-specific lymphadenitis ($n=58$), lymphoma ($n=22$), metastatic lesions ($n=19$) and leukaemia ($n=10$).

The commonest age group involved by tubercular lymphadenitis in this study was 21–30 years (30 per cent) followed by 11–20 years (27 per cent); the male:female ratio was 1·1·2. Fifty-eight patients (73 per cent) were of low socioeconomic status whereas 23 and 8 per cent of patients respectively were from middle and high economic groups.

The cervical lymph nodes were most frequently involved by tuberculosis, followed by the inguinal and axillary nodes (*Table 2*); 55 per cent of the cases presented with the typical features of matting and fixity of the nodes to the surrounding structures while the nodes were discrete in 18 cases. Abscess formation and discharging sinuses were noted in 15 and 13 per cent of cases respectively. The majority of the cases (78 per cent) presented within 4 months of onset of illness Besides lymph node enlargement in all patients, weight loss was noted

Table 1 *Dosages used for antituberculous chemotherapy*

	Dosage		
Drug	Adults <50 kg body-weight (mg day^{-1})	Adults ⩾50 kg body-weight (mg day^{-1})	Children (mg kg^{-1} body-weight day^{-1})
Rifampicin	450	600	15
Isoniazid	300	300	15
Ethambutol	800	1000–1200	25

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Table 2 *Site of involvement of lymph node groups*

Site of involvement	No. of cases	
Cervical group		
Occipital	3	56 (70)
Preauricular	1	
Submandibular	8	
Submental	2	
Jugulodigastric	23	
Jugulo-omohyoid	7	
Mixed	12	
Axillary group	5 (6)	
Inguinal group	7 (9)	
Multiple sites	12 (15)	
Total	80 (100)	

Values in parentheses are percentages

in 85 per cent, fever in 40 per cent and night sweats in 37 per cent. Ten per cent of the patients suffered from cough with occasional haemoptysis. The ESR was raised in all but six cases and was a useful index during follow-up. The Mantoux test was positive in 74 per cent of cases. Associated pulmonary lesions were detected in four cases only.

Fine needle aspiration cytology gave a positive diagnosis in 83 per cent of cases in this study, a false negative result in 14 per cent and equivocal results in 3 per cent; the technique did not result in complications Biopsy of the largest node gave histopathological confirmation in all cases; 80 per cent of patients had caseating and 20 per cent had non-caseating lesions. Culture in Lowenstein–Jensen medium showed that 65 per cent cases were positive for *Mycobacterium tuberculosis* of human type.

Short-term chemotherapy (for 3 months) remitted in 30 per cent of patients having no remaining nodes of more than 5 mm in diameter. After 6 months, 80 per cent had reduction of nodes below this size By the end of 9 months only 9 per cent had nodes of more than 5 mm in diameter, but they had normal ESR, weight gain and were symptom-free Surgery, apart from biopsy, in any form was not used in the present series even in the presence of non-healing ulcers, discharging sinuses or cold abscesses where aspiration only was performed Residual nodes, unhealed scars and sinuses disappeared within 6 months of follow-up. Toxic effects of any drug were not marked in any case and to date we are not aware of any form of recurrence.

Discussion

Peripheral lymph node tuberculosis is one of the commonest manifestations of extrapulmonary tuberculosis and one of the commonest diseases affecting peripheral lymph nodes. Its incidence in Asia and Africa has not decreased significantly despite an increased standard of living in the general population[1].

Most of our patients were in the second and third decade of life and we noted a slight female preponderance, as reported by others[1,2,3]. This may be because females in the age groups of 11–30 years are more conscious of their appearance and so present early. Also, the females in our male-dominated society have a low nutritional status and are exposed to overcrowding more than males.

The dominance of the neck nodes in tuberculosis has been established by many authors[1,4,5,6] and may be due to infection of the tonsils, adenoids and Waldeyer's ring, providing an early portal of entry. This finding is consistent with the view of Murty Madhusuden[7] that in Indian patients the portal of entry may be by inhalation and deposition of *M. tuberculosis* in the pharyngeal wall leading to upper deep cervical node involvement.

Matting and fixity of lymph nodes to surrounding structures was present in 55 per cent of our cases; others have observed matting of lymph nodes in 66–79 per cent of cases[2,4,7]. Matting is due to periadenitis and is an important diagnostic criterion. In late and untreated patients abscess formation and discharging sinuses were also observed with weight loss, fever and night sweats. The Mantoux test was positive in 74 per cent of our cases whereas Pamra and Mathur[4] and Purohit *et al.*[8] obtained positive reactions in 86 and 72 per cent of cases respectively.

Associated pulmonary lesions in all of our four cases were confirmed by positive sputum for acid-fast bacilli and by radiology. This low incidence may be because of the development of high immunity owing to wide environmental exposure to the disease.

Fine needle aspiration cytology gave a positive diagnosis in 83 per cent of our cases, a false negative result in 14 per cent and doubtful results in 3 per cent of cases; there were no false positive results. Others have obtained similar results[9–11]. This high accuracy of diagnosis reflects the fact that the whole gland is usually affected by the time the patient presents In our practice, biopsy is always undertaken to confirm the diagnosis and to determine whether the lesion is caseating or non-caseating The non-caseating or lymphadenoid type of change is the earlier phase of the disease but the histological picture does not alter the treatment or prognosis in any way Although culture of the gland in Lowenstein–Jensen medium confirmed the diagnosis in 65 per cent of cases in this study, a negative culture does not exclude the diagnosis as all enlarged lymph nodes do not necessarily contain live bacilli. Krishnaswamy *et al.*[1] and Campbell and Dyson[12] obtained positive cultures in 79 and 62 per cent of cases respectively.

Short-term chemotherapy was highly satisfactory as far as obvious reduction of the disease process was concerned and offered an apparent cure rate of 91 per cent in our series. A similar (90 per cent) result was obtained by Tripathy[13] using this regimen. Surgery with chemotherapy has yielded the same results as chemotherapy alone but in addition carries all the risks of any surgical procedure.

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Comparison of flow cytometry with static densitometry in papillary thyroid carcinoma

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The prognostic accuracy of flow cytometric and static densitometric DNA analysis was compared in 31 patients who had undergone surgery for papillary thyroid carcinoma between 1959 and 1978 (median follow-up 18 years). There were five deaths from papillary thyroid carcinoma. Three of six patients with DNA aneuploid tumours on flow cytometry died ($\mathrm{P}>0{\cdot}05$, *Fisher's exact test) compared with four of eight patients whose tumours were found to be aneuploid by static densitometry* ($\mathrm{P}<0{\cdot}02$). *When quantitative analysis was applied to the static densitometry data, all five patients who died from papillary carcinoma were distinguished, with no false positives* ($\mathrm{P}<0{\cdot}002$). *The prognostic accuracy of flow cytometric DNA analysis is less than that of static densitometry in which morphological selection of malignant cells permits quantitative measurements. DNA analysis may add refinement to existing scoring systems in predicting the risk of death from papillary thyroid carcinoma. Such information could provide the basis for controlled prospective evaluation of bilateral resection as opposed to lobectomy in defined high risk patients. At present there is insufficient evidence upon which aneuploidy should be used as a determinant of the extent of operation for papillary thyroid carcinoma.*

Keywords: DNA aneuploidy, papillary thyroid carcinoma, flow cytometry, static densitometry

Differentiated thyroid carcinoma has a predominantly good prognosis with 20-year survival rates of 80–90 per cent for papillary thyroid carcinoma[1,2]. Several risk factors have been identified including age[3–8,11], local tumour extension[1,3,5,9,10,11], tumour size[9,10], histological grade[9], marked cellular atypia[12] and metastatic disease[9,10,11].

An independent prognostic role for DNA aneuploidy in thyroid carcinoma was first reported from Sweden in 1984[13]. In a retrospective static cytometric study of patients with papillary carcinoma a clear difference between the nuclear DNA content of survivors and non-survivors was shown. More recently DNA aneuploidy has been reported by the Swedish group to be of similar prognostic accuracy in follicular[14] and medullary carcinoma[15].

Static cytometry is a time-consuming, microscope-based technique in which the DNA content of a small number (100–250) of morphologically identified cells is measured. Flow cytometry is a rapid method of analysing the DNA content of a large number of cells and reports from several centres suggest that static and flow cytometry give comparable results with regard to DNA ploidy[16–19].

A retrospective study was carried out to compare the prognostic accuracy of flow cytometric DNA analysis with static densitometry in a group of patients with long-term follow-up after operation for papillary thyroid carcinoma.

Patients and methods

Seventy patients in whom a diagnosis of papillary thyroid carcinoma had been made in the 20-year period from 1959 to 1978 were identified from pathology records. Haematoxylin and eosin stained sections from all available archival blocks were reviewed: in 13 cases the diagnosis of papillary carcinoma was either not confirmed or areas of anaplasia led to a revised diagnosis of anaplastic carcinoma These cases were excluded Of the remaining 57 patients, 23 were excluded: one died in the period immediately after operation and four patients died from unrelated causes within a year of operation In 11 cases either hospital records or tissue blocks had been lost or destroyed by fire and in seven patients (several of whom had left the area) follow-up data were not obtainable. Thirty-four patients remained with a definitive diagnosis of papillary carcinoma and with detailed follow-up information. The tumours were classified histologically as well differentiated or as moderately or poorly differentiated and cytologically as of low grade or of active or aggressive cellularity. Males aged 40 years and over and females aged 50 years and over were considered to be in a high risk age group

All patients had undergone surgery Total thyroidectomy had been performed in five patients, the remainder having undergone a lesser procedure. In one patient biopsy only was carried out, the tumour having been judged locally inoperable. In two patients the tumour had breached the thyroid capsule with local extension. One patient was known to have had distant metastases at the time of operation. Block dissection of lymph nodes was not performed but all visible and palpable nodes were removed. Nodal involvement was confirmed histologically in seven patients (21 per cent).

Flow and static cytometry were undertaken without prior knowledge of outcome

Flow cytometry

An archival block containing the most aggressive area of tumour was selected after examination of contiguous haematoxylin and eosin stained sections from all available material. If large areas of normal thyroid tissue were present on the block these were masked when sections were taken.

Preparation of single cell suspensions from paraffin-embedded tissue was carried out according to the method of Hedley *et al.*[20].

Staining was carried out using propidium iodide by a modification of the detergent–trypsin method of Vindelov *et al.*[21,22] and flow cytometric DNA analysis was carried out on an EPICS C flow cytometer[23] (Coulter Electronics, Florida, USA). Linear red fluorescence was displayed as a histogram and analysed using the software package available for the EPICS C. The coefficient of variation was measured in each case and a coefficient >10 was considered unacceptable The first major peak was assumed to represent DNA diploid nuclei[20] Aneuploidy was defined as the presence of a second peak clearly distinct from the first population In aneuploid tumours the DNA index was calculated from the ratio of the modal channel numbers Cell cycle analysis was performed using computer software (PARA 1, Coulter Electronics) on all tumours with a diploid DNA distribution pattern on flow cytometry.

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Table 1 *Deaths in patients with papillary thyroid carcinoma*

Patient no.	Age (years)	Sex	Survival (years)	Cause of death
1	73	F	7	Bronchopneumonia
2	73	F	4	Thyroid carcinoma
3	28	M	13	Road traffic accident
4	80	M	3/12	Thyroid carcinoma
5	74	F	7/12	Thyroid carcinoma
6	52	F	9	Thyroid carcinoma
7	63	F	19	Acute leukaemia
8	60	M	15	Myocardial infarction
9	70	M	5	Thyroid carcinoma
10	40	F	19	Bronchogenic carcinoma

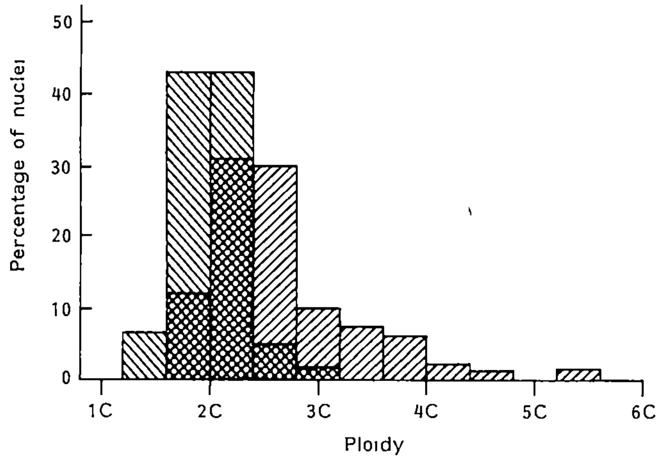

Figure 1 *Tumour qualitatively diploid by static densitometry, i.e. modal value between 1·6C and 2·4C. Quantitative analysis showed 72 per cent of nuclei with a DNA content >P90. The patient, an 80-year-old man, died from papillary carcinoma.* ▧, *Control nuclei;* ▨, *tumour nuclei*

Static cytometry

From each case a single paraffin block was selected in which the most aggressive area of the tumour was represented. Two 4 μm sections were cut and Feulgen stained according to the method of Gaub *et al.*[24] Static cytometric measurements were made using a Vickers M85 scanning microdensitometer (wavelength 546 nm, Vickers Instruments, York, UK). Reference to a contiguous haematoxylin and eosin stained section allowed orientation of the Feulgen section. Fifty tumour cells and 30 control cells were measured on each of the two slides and the results were combined. The tumour nuclei were selected on the basis of cytological features of aggression (nuclear size, nuclear pleomorphism and stain intensity). Normal thyroid cells were used as controls whenever possible but when no normal thyroid tissue was present in the paraffin section lymphocytes and polymorphs were measured.

Data were analysed in two ways

1. Qualitative analysis; the 2C (diploid) value was calculated from the mean of the control nuclei and the data for control and tumour nuclei were graphed in increments of 0·4C

2. Quantitative analysis; the percentage of tumour nuclei with a DNA content greater than the 90th percentile (P90) of the control nuclei was calculated and recorded as the percentage of DNA aneuploid nuclei.

Results

There were 27 female patients and seven male patients with an age range of 6–82 years (median 40 years). Fourteen patients were in the high risk age group and 20 were in the low risk group.

Twenty-four tumours (71 per cent) were histologically well differentiated and ten (29 per cent) were moderately or poorly differentiated. Twenty-two tumours (65 per cent) were classified as having low grade cellular activity and 12 (35 per cent) had active or aggressive features.

Ten patients (29 per cent) were dead at the time of follow-up: five deaths were unrelated and five were directly attributable to thyroid carcinoma (*Table 1*). The duration of follow-up in survivors ranged from 8 to 23 years (median 18 years, mean 16·5 years).

Flow cytometry

Adequate cell numbers for flow cytometric analysis were obtained in all cases. In three cases the DNA histograms obtained were repeatedly unsuitable for analysis (coefficient of variation >10) and these cases were excluded from measurement of DNA ploidy and cell cycle analysis. Twenty-five of the remaining 31 cases (81 per cent) had a unimodal DNA distribution. In these 25 cases the proliferative index (the percentage of cells in $S+G_2$ phases) ranged from 10 to 42 per cent (median 25 per cent). The full peak coefficient of variation ranged from 5·6 to 9·9 (mean 7·8). Six of the 31 cases (19 per cent) were found to have a bimodal DNA distribution and were therefore DNA aneuploid.

Static cytometry

Only data from the 31 cases with acceptable flow cytometric histograms were considered:

1. Qualitative analysis showed that in 23 cases the modal DNA peak lay between 1·6 and 2·4C (diploid) (*Figure 1*). In six cases the modal value was greater than 2·4C (hyperdiploid) (*Figure 2*) and in two cases it was less than 1·6C (hypodiploid) (*Figure 3*).

2. Quantitative analysis showed that the percentage of tumour nuclei with a DNA content greater than the 90th percentile of control nuclei (P90) ranged from zero to 84 per cent (median 21 per cent).

There was no correlation between the percentage of DNA aneuploid nuclei from quantitative static cytometry and the proliferative index on flow cytometry ($r=0{\cdot}132$).

Prognosis

All five patients who died from papillary thyroid carcinoma were in the high risk age group (five out of 14 patients, $P<0{\cdot}02$) and all had active or aggressive cytology (five out of 12 patients, $P<0{\cdot}01$). There were three deaths in the ten patients with poorly differentiated histology and two in the 24 with well differentiated histology ($P>0{\cdot}1$).

On flow cytometric analysis three of the six patients (50 per cent) with DNA aneuploidy died compared with two of the 25 patients (8 per cent) with diploid tumours ($P>0{\cdot}05$, Fisher's exact test). Of the three survivors with an aneuploid tumour two were in the low risk age group.

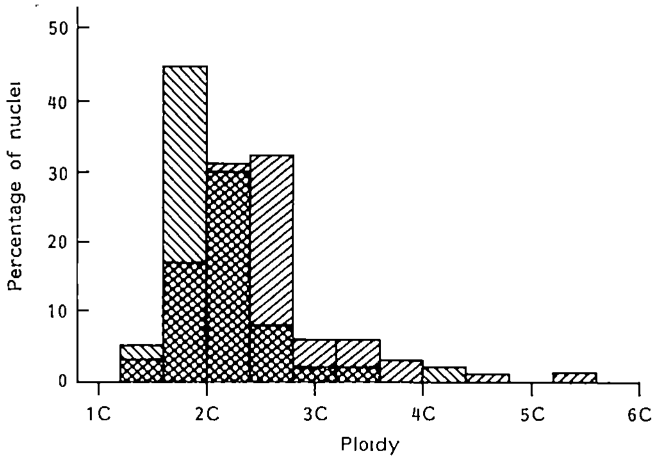

Figure 2 *Tumour qualitatively aneuploid by static densitometry, i.e. modal value >2·4C. Quantitative analysis showed only 27 per cent of nuclei with a DNA content >P90. This 6-year-old female patient is a survivor* ▧, *Control nuclei;* ▨, *tumour nuclei*

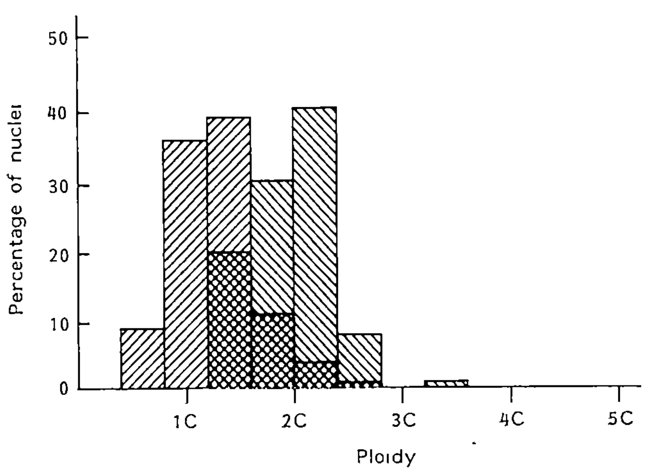

Figure 3 *Tumour qualitatively hypodiploid by static densitometry, i e. modal value <1·6C. Quantitative analysis showed 1 per cent of tumour nuclei with a DNA content >P90. The patient, a 37-year-old woman, is a survivor.* ▧, *Control nuclei;* ▨, *tumour nuclei*

When the ploidy determined from the modal DNA value by static cytometry was considered, four of the six patients with hyperdiploid values died. One of 23 patients with a diploid pattern died and both patients with hypodiploid patterns survived. A clear separation of survivors and non-survivors was not present on qualitative densitometry although DNA aneuploidy was still a powerful prognostic factor· four of eight patients with non-diploid tumours died from thyroid carcinoma (50 per cent) compared with one of 23 with diploid tumours (4 per cent) ($P<0·02$).

On quantitative static cytometry all non-survivors had a percentage DNA aneuploidy greater than 58 per cent. All survivors, i.e. those alive and well at the time of follow-up or who died from other causes, had a percentage DNA aneuploidy less than 46 per cent (*Figure 4*).

Discussion

Static densitometric measurement of nuclear DNA content on a quantitative basis was found to distinguish clearly between death and survival from papillary thyroid carcinoma. The absolute separation of non-survivors (DNA aneuploidy >58 per cent) and survivors (DNA aneuploidy <46 per cent) (*Figure 4*) mirrors the Swedish findings[13].

DNA aneuploidy determined by flow cytometry was an adverse prognostic factor; 50 per cent of patients with DNA aneuploid tumours died compared with 8 per cent of patients with DNA diploid tumours. This six-fold increased risk of death from thyroid carcinoma in patients with aneuploid tumours was, however, not statistically significant ($P>0·05$).

Previous workers have reported a good correlation between DNA ploidy measured by static and flow cytometry[16–18]. In this study the prognostic accuracy of quantitative static densitometry was much greater than that of flow cytometry.

Conventionally the results of static cytometry have been analysed qualitatively with DNA aneuploidy being recorded when the modal value of tumour cells exceeds 2·4C, where 2C is calculated from the mean of the control values[16,18].

The ploidy status from qualitative static and flow cytometry was in agreement in four cases of DNA aneuploidy and in 21 cases of DNA diploidy, i.e. concordance in 25 cases. Disparity was observed in six cases. Four patients were aneuploid by qualitative static cytometry while diploid by flow cytometry and two were aneuploid by flow cytometry although diploid by qualitative static cytometry.

Several factors may contribute to this disparity. In all single cell suspensions prepared for flow cytometry DNA diploid cells are present. These include non-tumour cells and diploid tumour cells even in aneuploid tumours[17]. The resolution of two modal DNA peaks depends on the coefficient of variation, the percentage of aneuploid nuclei and the DNA index (i.e. the ratio between aneuploid and diploid peaks)[23,25]. With a mean coefficient of variation of 7·8, as achieved in fixed tissue disaggregates, DNA aneuploid peaks are obscured when the DNA index is <1·3 (Reference 23). A lower coefficient of variation is achieved with fresh tissue and most previous comparative studies have utilized fresh material[16–18,26]. A single comparative study using archival material[19] demonstrated a good correlation between flow and static cytometry but the aneuploid peak occurred at greater than 3C in all cases.

In static cytometric studies morphological selection of tumour and control cells increases the percentage of aneuploid cells included in the analysis of an aneuploid tumour and permits definition of the control population. Static cytometry allows detection of shifts in the modal position before the resolution of two separate modes in a mixed population is possible by flow cytometry.

In contrast some tumours are DNA aneuploid by flow cytometry but diploid on static densitometric analysis which may reflect unrepresentative morphological selection of the small sample of 100 cells Flow cytometry includes non-tumour cells but involves a much larger cell sample (10 000) and is likely to be more representative of the whole tumour. Flow cytometry permits detection of cell subpopulations provided a low coefficient of variation is achieved.

The majority of static cytometric studies, including those that have included comparison with flow cytometry, have been based on the random selection of cells for analysis. Sensitivity is greatly increased, however, when cells are selected for analysis on morphological criteria[26]. The presence of cytological features of aggression is an important prognostic factor in papillary thyroid carcinoma[11] and may relate to the high degree of aneuploidy noted when these features are used to select cells for DNA measurement.

We have confirmed the Swedish finding[13] that quantitative static cytometry of archival material is correlated with the outcome in papillary thyroid carcinoma. Qualitative static densitometry and flow cytometry were less accurate. Although flow cytometry is a much more rapid procedure than static densitometry it does not lend itself to quantitative analysis. The inevitable presence of an unknown percentage of non-tumour cells in any cell suspension means that greater accuracy will depend on the development of methods allowing cell selection.

From a clinical point of view there are two important

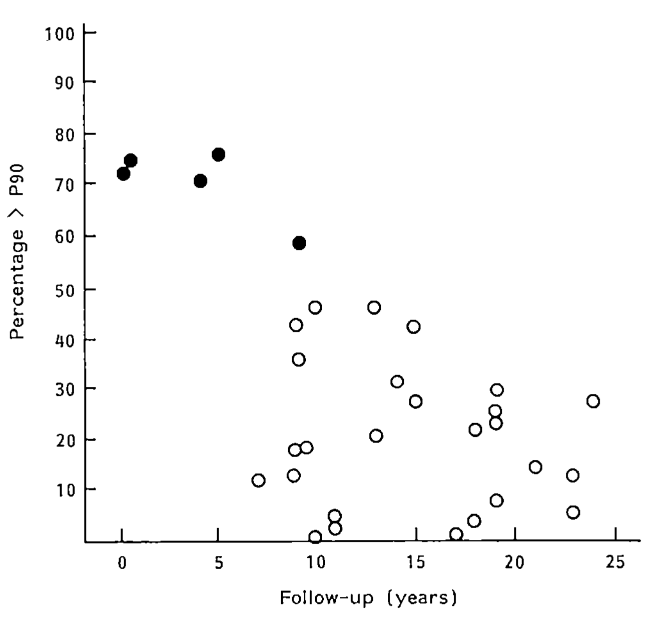

Figure 4 *Quantitative static densitometry and survival. All non-survivors (●) had >58 per cent of nuclei with a DNA content >P90. All survivors (○) had <46 per cent of nuclei with a DNA content > P90*

questions. First, does cytometry, which is both time consuming and expensive, give prognostic information that is not more simply obtained from scoring systems and, second, would such information provide a basis for tailored management according to risk? Recently several scoring systems have been devised based on multifactorial analysis of risk factors from retrospectively gathered data[9,10,12]. These allow separation of patients into low and high risk groups with 25-year mortality rates of 2 and 46 per cent respectively[9,10] on the basis of age, tumour size, tumour spread and histology. When the system of Hay and colleagues[9] was retrospectively applied to our group of patients its accuracy was found to approach that of quantitative static densitometry. Six patients were scored as high risk and these included all five non-survivors The remaining 25 patients, all of whom survived, were scored as low risk.

Although both static and flow cytometry may be performed on thyroid aspirates to give prognostic information before operation this is not a great advantage since patients may be readily scored at the time of operation by Cady and Rossi's system[10] which does not include histology as a factor Even with systems that do include histology it is claimed that a patient's prognostic score may be calculated at the time of operation[9]. At present only retrospective studies of the relationship between DNA aneuploidy and outcome in papillary thyroid carcinoma have been reported and prospective studies will be very long term. None the less it is a reasonable presumption that relationships established from archival material will be reproducible prospectively. It is also probable that ploidy status, preferably according to static densitometry, would add additional accuracy to scoring. Such information would provide the basis for long-term prospective multicentre controlled evaluation of different forms of management in high risk patients with papillary carcinoma.

The continuing controversy between total thyroidectomy, lobectomy plus contralateral subtotal resection, and lobectomy alone in differentiated thyroid carcinoma has recently been discussed by Hay and colleagues[9] and Cady and Rossi[10]. Retrospective analysis of outcome in 860 patients with papillary carcinoma treated at the Mayo Clinic from 1946 to 1970 showed improved survival in high risk patients undergoing bilateral resection compared with lobectomy alone although the difference was not statistically significant. Total thyroidectomy was associated with a significantly higher cancer-related mortality rate than bilateral subtotal or near total thyroidectomy although this may be explicable if patients undergoing total thyroidectomy had more aggressive disease[9].

It is becoming clear that the majority of patients with papillary carcinoma are adequately treated by lobectomy. In addition there are some patients with clinically obvious bilateral disease in whom contralateral resection, although possibly not total thyroidectomy, is indicated for local disease control. There may also be a case for bilateral resection as Cady and Rossi[10] suggest in the small number of patients at high risk according to scoring. We do not think on present evidence that aneuploidy *per se* should be used as a determinant of more aggressive treatment as opposed to a basis for prospective comparison. Finally, as a general observation in many forms of cancer, conviction that more radical local treatment results in improved survival in patients who have biologically aggressive disease is dissipating and it would be anomalous if differentiated thyroid carcinoma were to prove an exception.

Acknowledgements

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Unremarkable parotid tumours that prove to be malignant

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Of 539 patients with clinically unremarkable lumps treated by formal parotidectomy, subsequent histological examination indicated that 20 of these lesions were malignant. After a follow-up of 1–18 years, only one patient has suffered a recurrent tumour and none has died from disease related causes. The results indicate that formal parotidectomy is an acceptable means of treating the small number of malignant tumours presenting in this way, and strengthen the argument that attempts to obtain a histological diagnosis before treatment are contraindicated.

Keywords: Parotid, neoplasms, parotidectomy

Nearly all malignant parotid tumours present as solitary lumps, but the majority also demonstrate signs (facial nerve weakness, attachment to skin or bone), indicating that the lump cannot be a benign tumour of parotid origin However, a small group of malignant tumours present merely as unremarkable lumps in the parotid region without these signs. Over 50 per cent of clinically benign parotid lumps prove to be pleomorphic adenoma[1]. The management of such lumps has been the subject of much debate Theoretically, preliminary biopsy of these lumps even by fine needle aspiration predisposes to recurrence by breaching the capsule. We find it difficult to understand how fine needle aspiration cytology can be accurate in the parotid gland where nearly all the varieties of tumour originate from two single stem cells, the myoepithelial cell and the ductal epithelial cell[2–4]. Treatment by enucleation rather than formal parotidectomy is prone to recurrence, and postoperative radiotherapy has never been convincingly shown to reduce recurrence rates[3,5–7]. Such recurrences would be even more serious in the situations where the tumours proved to be more malignant than pleomorphic adenoma. If formal parotidectomy were to prove inadequate for the treatment of unremarkable malignancies by allowing a high recurrence rate, there would be a need to try to obtain preoperative histological or cytological diagnosis However if formal parotidectomy was adequate, this would strengthen the argument in favour of formal parotidectomy as the management of all unremarkable lumps, and attempts at preoperative diagnosis would therefore be unnecessary and possibly meddlesome.

The term 'formal parotidectomy' may need some explaining. It implies that the intention, as early as possible in the operation, is to display the facial nerve and its branches throughout their course within the parotid gland. The goal is to remove the lump with the widest possible margin of normal tissue[8]. However, the term also implies that the surgeon is prepared to sacrifice one or more branches of the facial nerve or even the trunk itself if the lump is assessed by touch to be invading the relevant nerves. If all the named branches (including at least one buccal branch) are left anatomically intact, the operation is called a conservative parotidectomy. If one or more branches is divided, the operation is semi-conservative and if the whole nerve is destroyed the operation is radical parotidectomy. In most patients the lump is superficial to the facial nerve and superficial parotidectomy is performed For lumps in the deep lobe an extended superficial (part of the deep lobe removed in continuity with the superficial lobe) parotidectomy is necessary Each formal parotidectomy ends as either conservative, semi-conservative or radical and may be superficial, superficial extended, or total.

Patients and methods

Between 1968 and 1988, 539 patients with previously untreated unremarkable parotid lumps (i e a lump in the parotid region with no other signs or symptoms), were treated in our department by formal parotidectomy without preliminary biopsy. Twenty of these patients, however, proved to have tumours more malignant than pleomorphic adenoma. All the data were entered onto index-cards prospectively and subsequently transferred to a computerized data base for ease of analysis The patients records were studied for recurrences and disease-related deaths in order to determine how successful this policy had been

Results

The group comprised five patients with mucoepidermoid tumour, four with acinic cell tumour, seven with adenoid cystic carcinoma and four with various histological variants of 'frank carcinoma' (*Table 1*). Formal parotidectomy was performed in all these patients. The parotidectomy was conservative in 12 cases, semi-conservative in six cases and radical in two cases

Only in two cases were there residual or recurrent tumours. One patient had a recurrent mucoepidermoid tumour following histologically incomplete excision and postoperative radiotherapy, but after a local excision of this recurrence has been disease free for 6 years. The other patient had extensive adenoid cystic carcinoma involving the pharynx but the residual tumour following total radical parotidectomy appears to have been well

Table 1 *Results of formal parotidectomy in 20 patients with tumours more malignant than pleomorphic adenoma*

Histology	*n*	Follow-up duration (years)	No of incomplete excisions	No of recurrences	No. of disease related deaths
Mucoepidermoid tumour	5	1–7	1	1	0
Acinic cell tumour	4	3–10	0	0	0
Adenoid cystic carcinoma	7	1–18	1*	1*	0
Frank carcinoma	4	1–5	0	0	0

* Residual tumour

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controlled by radiotherapy. The remaining 18 patients had histologically complete excisions and have had no recurrences to date. Patients with adenoid cystic and frank carcinomas received postoperative radiotherapy as a matter of routine. There have been no disease-related deaths. Permanent facial nerve palsy was only seen in cases where the surgeon had deliberately sacrificed branches of the nerve in order to obtain adequate clearance. Four out of six patients who had each undergone sacrifice of one major division of the nerve developed permanent facial nerve palsy of the denervated territory, the two patients who had destruction of the whole nerve both developed a complete and permanent facial palsy. Two patients who merely had division of the buccal branches had no residual palsy.

Discussion

The conundrum expressed in the introduction is a difficult one. It seems obvious at first sight that a lump which might be a neoplasm should be assessed by every means possible, including histology, so that a decision about definitive treatment is made in the light of the maximum information. On the other hand, we have been impressed by the frequent morbidity resulting from recurrence of so-called benign parotid tumours when the original operation had been an inadequate local excision or an excision preceded by open or needle biopsy[9]. The dangers of inadequate excision and the strong tendency to implantation recurrence are well documented[10].

Proponents of fine needle aspiration cytology are convinced that the small calibre of the needle prevents dissemination of tumour cells. They may be right, but so far they have not published data that demonstrate how useful the technique is in decision making, i.e., how often the technique altered the decision in management. In any case the failure to document recurrences becomes less significant when one realizes that half the recurrences after inadequate surgery take more than 10 years to become manifest[9]. The alternative is to perform an excision biopsy of an unremarkable lump with the widest possible margin of normal tissue, the facial nerve being preserved provided that the lump is not invading the nerve (formal parotidectomy). This policy gives excellent results in the case of the commonest lesion, the pleomorphic salivary adenoma[11,12]. There are two theoretical disadvantages of this policy. first, the excision may constitute a therapeutic overkill for such lesions as lipoma or tuberculous lymphadenitis and this will be addressed in a separate paper; second, some unremarkable lumps turn out to be malignant. Did the formal parotidectomy approach commit the surgeon to a form of treatment less radical than necessary and jeopardize the patient's chances of a successful outcome? The answer to this question seems to depend on the two facts demonstrated in this paper namely that: the chance of malignancy is only 20/539 or 3·7 per cent, and that in 20 such patients there has been no disease-related death in a follow-up ranging from 1 to 18 years (median 5 years). In the one patient with extensive adenoid cystic carcinoma there is no indication that preliminary biopsy and a wider excision would have yielded a better result, although this must be accepted as a possibility. So only one of the 20 patients might have possibly expected a better result by the alternative line of management. One in 20 (5 per cent) of 3·7 per cent is 0·185 per cent. Although the period of follow-up is relatively short, we believe that these results strengthen the case for formal parotidectomy without prior attempts to obtain histological diagnosis in patients with unremarkable parotid lumps.

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Asymmetrical nature of the muscular anatomy of the infantile pylorus: a possible consideration in pyloromyotomy

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Post-mortem studies of the normal infantile pylorus have demonstrated an asymmetrical structure with the mucosa protruding under the circular muscle at the lesser curve but not on the anterior surface. In addition the circular muscle was often discontinuous at the pyloroduodenal junction with only longitudinal fibres or even fibrous tissue separating the mucosa from the serosa. In a further specimen in which a pyloromyotomy had been performed 10 weeks previously, this asymmetry was more pronounced. This anatomy suggests that in pyloric stenosis it may be safer to site the caudal part of the pyloromyotomy incision on the anterior surface, rather than on the anterosuperior surface as most authors recommend. Perforation of the mucosa is predicted to be less likely.

Keywords: Pylorus, pyloric stenosis, pyloromyotomy

Among surgeons the common concept of the pylorus is of a uniform structure such as that shown in *Figure 1*. Therefore, when operating in the area it is assumed that there is no regional or sector variation in structure that may be pertinent to surgical technique. However, when preparing control tissue for studies on pyloric stenosis[1], and on reading the associated literature[2,3], it was appreciated that the muscular anatomy is more subtle than the commonly-held concept. This may have implications regarding the safest site for pyloromyotomy in pyloric stenosis.

Congenital pyloric stenosis is a common condition of early infancy resulting in projectile vomiting until relieved by pyloromyotomy. While the mortality rate of pyloromyotomy has essentially been eliminated, there remain minor morbidity problems[4–10]. One of these is the operative complication of perforation of the duodenal mucosa during complete splitting of the circular muscle. The incidence of this complication varies from 0·5 per cent to 11·5 per cent[5,6,8,10]. The usual recommendation is to site the pyloromyotomy incision towards the lesser curve on the anterosuperior avascular area of the thickened pylorus[4,7,9,11–13]. The purpose of this study was to further investigate the normal infantile pyloric structure.

Patients and methods

The pyloric area was removed from 12 infants who had died from sudden infant death syndrome. The age range was 1–6 months. In an attempt to ensure there was minimal fixation artefact, ties were placed around the antrum as well as the duodenum, after which the lumen was perfused with 4 per cent formaldehyde and the specimen immersed in the same fixative. In seven specimens longitudinal strips were cut from the four quadrants and macroscopically examined, after which the strips were processed for microscopy. In five cases, the mucosa was carefully dissected off unfixed specimens, which had been opened along the greater curve or on the posterior surface, to reveal the form of the muscular architecture.

A further infant, who had been operated on for pyloric stenosis some 10 weeks previously, had subsequently died from sudden infant death syndrome. The pyloric specimen was cut into longitudinal sections involving each of the four quadrants.

Results

When opened and viewed from the mucosal surface, the pyloroduodenal junction has the appearance of a ridge with some overhang of the pyloric mucosa (*Figure 2*). However, the underlying muscle is an asymmetrical structure with the circular muscle being much thicker at the lesser curve. In this area the smooth muscle protrudes into the duodenum (*Figures 2* and *3*). In contrast, the muscle on the anterior aspect of the pylorus does not protrude (*Figures 2* and *3*). This difference, noted in all 12 cases, was also present to a more pronounced degree in the specimen from the patient who had died from sudden infant death syndrome some 10 weeks after effective pyloromyotomy (*Figure 4*).

There was also often a discontinuity of the circular muscle at the pyloroduodenal junction. In these instances there were only a few longitudinal muscle fibres separating the serosa from the submucosa. This occurrence has been reported previously and referred to as 'pyloric block'[2].

Discussion

The normal human infantile pylorus is a complex structure with considerable circular muscle thickening at the lesser curve. This has been referred to as the torus and has been described in great detail by comparative anatomists[2,3]. The basic structure is present in many mammals and in the human from fetal life through to adulthood[3]. It provides the anatomical basis for the complicated sphincter function of the pylorus[14]. In addition there has been documentation of the incompleteness of the circular muscle at the pylorus, which is most pronounced in infancy[2]. The present work confirms the asymmetrical structure in a more detailed study involving the infant period and it

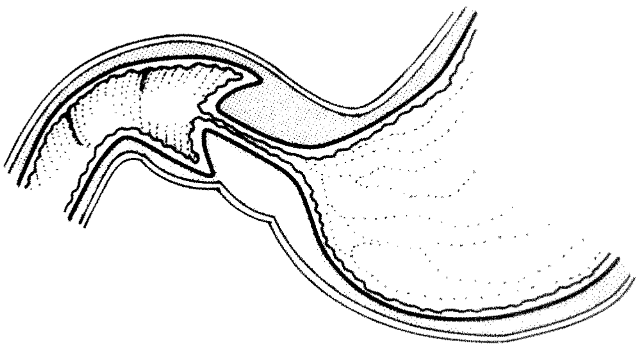

Figure 1 *Type of illustration commonly representing the structure of the human pylorus.* ▨, *circular muscle*

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clearly shows the infolding of the mucosa under the circular muscle at the region of the lesser curve as well as the frequent discontinuity of the circular muscle layer.

Clinical papers on pyloric stenosis have commented on the problem of mucosal perforations during the performance of pyloromyotomy[4–13]. Particular emphasis has been made of the 'critical site' of the folded duodenal mucosa that lies in a superficial position just distal to the end of the serosal incision[7,11]. Diagrams that have been used portray a uniform protrusion much like the vaginal cervix[7,11]. However this appearance, which is familiar in radiographs of the pylorus, reflects the mucosal folding and not the underlying asymmetrical muscular structure. The commonly recommended incision site on the anterosuperior surface is at an area where the circular muscle overhang and mucosal infolding are most

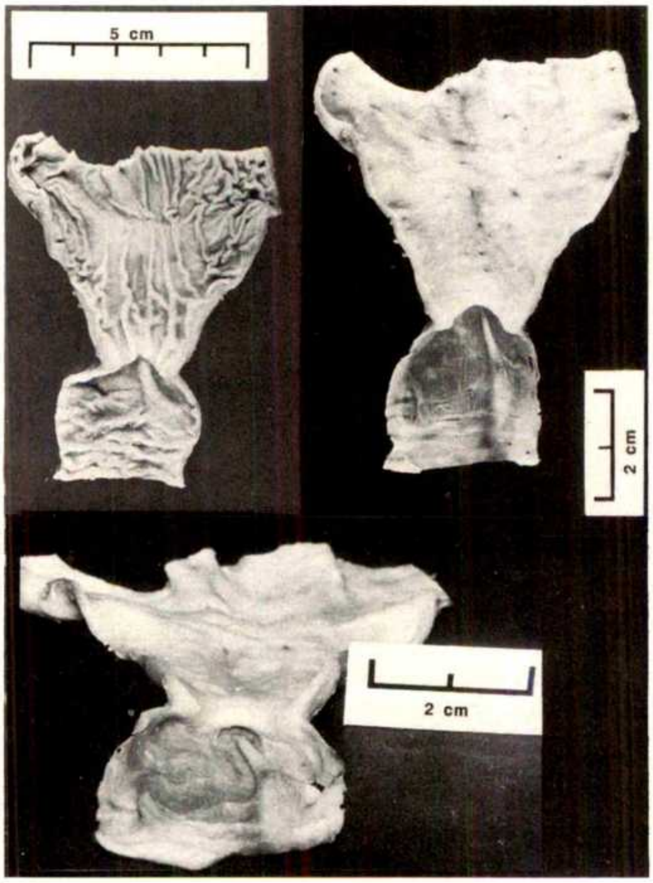

Figure 2 *Macroscopic appearance of the pylorus, opened along the greater curve. Top left: shows the mucosa intact. The mucosa forms a ridge that is slightly offset with the pyloroduodenal junction being slightly more distally placed at the greater curve. Top right: the mucosa has been removed to show the underlying muscular structure, which is a more pronounced arch. Bottom: oblique view to show the pronounced circular muscle overhang at the lesser curve area*

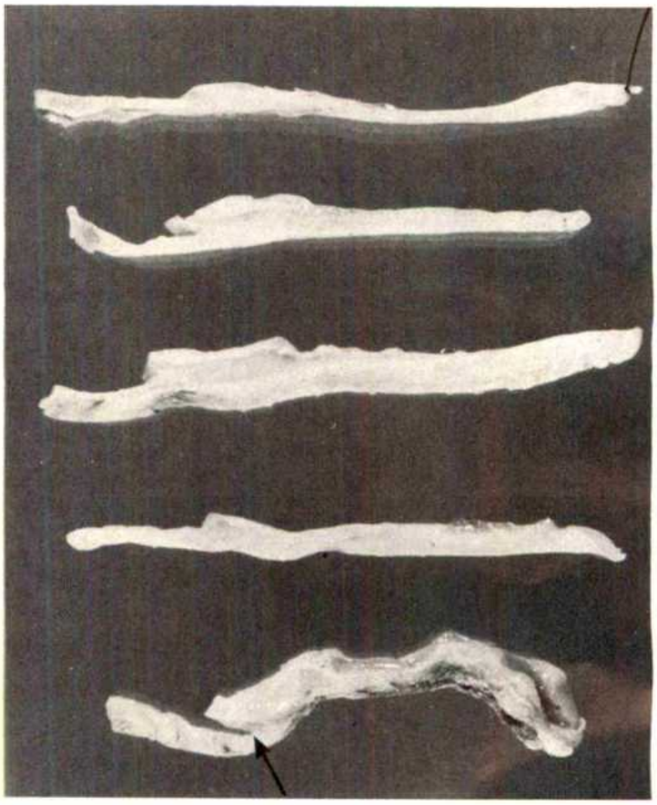

Figure 4 *The four quadrants in a patient who had been operated on for pyloric stenosis 10 weeks previously. The uppermost section is from a normal pylorus for comparison. The next four sectors, from the top down, represent the posterior surface, the greater curvature, the anterior surface and the lesser curve (where the invagination is most pronounced, arrowed)*

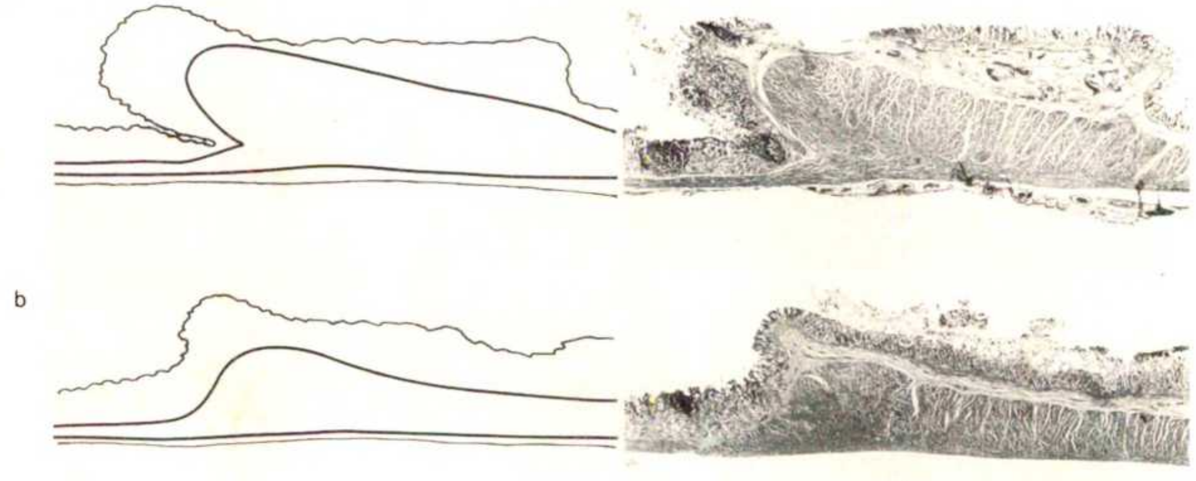

Figure 3 *Microscopic appearance at the lesser curve* **a** *and anterior surface* **b**. *The smooth line in the sketches represents the circular muscle. In both there is some mucosal and submucosal protrusion, but only at the lesser curve does the circular muscle protrude*

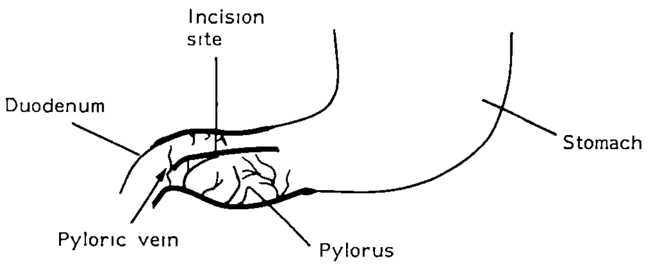

Figure 5 *An incision placed on the most anterior aspect of the avascular area and curving distally to avoid the invaginating mucosa. This should ensure minimal bleeding and lessen the risk of duodenal perforation*

pronounced. In contrast, on the anterior surface, the circular muscle does not overhang or protrude and the mucosa does not invaginate under the muscle. This difference in mucosal and muscular anatomy persisted in the post-mortem specimen from the patient who had been operated on for pyloric stenosis. Therefore, an incision made on the anterosuperior surface would theoretically be more likely to result in perforation whereas an incision on the anterior surface would carry a lesser risk Nevertheless, the anterior site has more serosal vessels and it may be inappropriate to incise at this location as postoperative bleeding, although rare, can be significant in patients with pyloric stenosis[15–18].

Considering both these factors, it is suggested that there may be an advantage in commencing the pyloromyotomy incision proximally in the avascular area, as far as is practical towards the anterior surface. In patients in whom the avascular area is located towards the lesser curve, the distal part of the incision should curve down onto the anterior surface (*Figure 5*). Not all distal circular muscle fibres need be divided. If the muscle on either side of the incision moves independently then the incision is sufficient.

It is possible that the post-mortem findings do not accurately represent the living anatomy and therefore have little relevance in the discussion of surgical technique. However, these findings have been demonstrated in several studies covering a wide range of specimens and are probably a true reflection of the intrinsic normal anatomy[3]. Less certain is the extrapolation to the pathological state which occurs in pyloric stenosis. Although the postoperative specimen did show a similar structure, it is possible there may be considerable variation in the degree and configuration of the muscular hypertrophy in pyloric stenosis. There is a need to study further specimens as well as to consider the use of intraoperative ultrasound to determine how consistent, and thereby how relevant, the observed structural anatomy really is.

A possible criticism of any consideration of refinement of technique is that the current method has stood the test of time However, although perforation is often considered an acceptable complication if immediately recognized, most paediatric surgeons consider it to be the result of poor technique and that the published incidence rates (0·5–11·5 per cent) are unacceptably high. Although pyloromyotomy is one of the classical operative procedures that has dramatically affected an otherwise fatal condition, there is still room for review.

This study describes the asymmetrical anatomical structure of the human pylorus and raises the possibility that this may be an important factor, along with instrumentation[10], in attempts to eliminate mucosal perforation during pyloromyotomy.

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Plasma chloride and alkalaemia in pyloric stenosis

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Fifty infants with infantile hypertrophic pyloric stenosis were studied prospectively to evaluate the reliability of plasma chloride estimation in the assessment of the acid–base status on admission and during correction of alkalaemia. Four cases were subsequently excluded because of a breach of the study protocol, leaving 46 cases in the study. Seventeen (37 per cent) were normoacidaemic on admission; 13 had plasma chloride concentrations of ≥106 mmol/l and four had chloride concentrations of 100–105 mmol/l on admission. Twenty-nine (63 per cent) were alkalaemic on admission; six cases had chloride concentrations of 100–105 mmol/l and 23 cases had concentrations of <100 mmol/l. Of those 29 cases requiring correction of alkalaemia, normoacidaemia was achieved at a plasma chloride concentration of ≥106 mmol/l in 21 cases (72 per cent) and at a concentration of 100–105 mmol/l in eight cases (28 per cent). Plasma chloride is a reliable parameter in the assessment and correction of alkalaemia in infantile hypertrophic pyloric stenosis provided that a concentration of at least 106 mmol/l is the goal.

Keywords: Pyloric stenosis, alkalaemia, plasma chloride

The biochemical disturbance in infantile hypertrophic pyloric stenosis is typically a hypochloraemic alkalaemia associated with dehydration. This is the result of persistent vomiting with a closed pylorus resulting in large losses of gastric secretions, mainly hydrochloric acid and smaller amounts of sodium and potassium as chloride salts.

The purpose of this study was to examine the correlation between the plasma chloride concentration and the degree of alkalaemia, and to determine if the plasma chloride concentration could be used as a reliable parameter in the assessment and correction of alkalaemia in infantile hypertrophic pyloric stenosis. No previous studies have examined this question although plasma chloride is used clinically for that purpose.

Patients and methods

Fifty consecutive infants with infantile hypertrophic pyloric stenosis were entered into a prospective study over a 2-year period. Four cases were excluded because of a breach of the study protocol; they either failed to have a plasma chloride estimation on admission or on completion of resuscitation

On admission, blood was taken for plasma sodium, potassium, chloride and standard bicarbonate estimation. The standard bicarbonate concentration on admission was not made available to the clinical staff Correction of the hypochloraemic alkalaemia and dehydration was carried out administering an intravenous infusion of 0 9 per cent saline solution containing 20 mmol/l of potassium chloride (approximately 170 mmol of chloride per litre of solution). A plasma chloride concentration of 100 mmol/l or more within 12–24 h was the goal when repeat estimation of plasma sodium, potassium and chloride was performed On achieving a plasma chloride concentration of ≥100 mmol/l, capillary acid–base (Astrup) status was estimated to determine whether correction of alkalaemia had been achieved When normoacidaemia was achieved arrangements were made to proceed to operation. Normoacidaemia was defined in this study as a standard bicarbonate of ≤26 mmol/l, which approximates to a base excess of ≤ +2 mmol/l.

Heparinized blood specimens were utilized because they yield a greater quantity of sample for analysis compared with clotted blood specimens, an obvious advantage in paediatric patients Plasma chloride was measured by the technique of coulometric titration. This technique does not involve ion selective electrodes and is not susceptible to interference by heparin[1,2].

Results

The male:female ratio was 4·5·1. The mean age was 45 days (range 16–150 days). The mean duration of vomiting was 8 days in the normoacidaemic group on admission ($n=17$) and 13 days in the alkalaemic group ($n=29$); a difference that does not achieve statistical significance. There were no cases of clinical tetany and no cases of post-anaesthetic apnoea.

The biochemical results on admission and following resuscitation are as shown in *Tables 1* and *2* respectively. In the normoacidaemic group ($n=17$) none had hypokalaemia; the lowest plasma potassium being 4·5 mmol/l. In the alkalaemic group ($n=29$), 15 per cent were hypokalaemic; plasma potassium concentrations below 3·5 mmol/l on admission.

Discussion

In infantile hypertrophic pyloric stenosis persistent vomiting results in large losses of gastric secretions, mainly hydrochloric

Table 1 *Biochemical parameters on admission*

		Plasma chloride (mmol/l)		
	Number	≥106	100–105	<100
Normoacidaemic	17 (37)	13	4	0
Alkalaemic	29 (63)	0	6	23
Total	46			

Values in parentheses are percentages

Table 2 *Biochemical parameters after resuscitation and correction of alkalaemia*

	Number	Plasma chloride (mmol/l)
	21 (72)	≥106
	8 (28)	100–105
Total	29	

Values in parentheses are percentages

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acid and smaller amounts of sodium and potassium as chloride salts. The typical resultant metabolic disturbance is a hypochloraemic alkalaemia with elevated plasma bicarbonate, associated with dehydration[3]. The plasma chloride concentration is used as a guide clinically in the assessment and correction of the biochemical disorder in these infants, based on the rationale that when hypochloraemia has been corrected so, presumably, would be alkalaemia. Because the commonly accepted normal adult reference interval for plasma chloride is 95–105 mmol/l the median concentration of 100 mmol/l has come to be accepted in clinical practice as a satisfactory concentration at which adequate resuscitation would be achieved. A chloride concentration of 90 mmol/l has been advocated by Hatch and Sumner as a satisfactory normal concentration[4]. Kumar and Bailey found that 38 per cent of their children with 'normal chloride concentrations' were alkalaemic. However, they regarded 90 mmol/l as a normal concentration[5].

We are not aware of any previous studies to determine the reliability of plasma chloride as a guide to the correction of alkalaemia in infantile hypertrophic pyloric stenosis. Our study shows that in the normoacidaemic group on admission ($n=17$), the plasma chloride concentration was $\geqslant 100$ mmol/l in all of them with 77 per cent of this group having a concentration of $\geqslant 106$ mmol/l and 23 per cent with a concentration of 100–105 mmol/l. In the alkalaemic group ($n=29$), correction of alkalaemia was achieved at a plasma chloride concentration of $\geqslant 106$ mmol/l in 72 per cent of cases and at a concentration of 100–105 mmol/l in 28 per cent.

Correction of alkalaemia before surgery is essential in the resuscitation of infants with infantile hypertrophic pyloric stenosis (together with correction of hypovolaemia and dehydration) because of the danger of post-anaesthetic apnoea occurring in alkalaemic infants[6]. In the alkalaemic state the low hydrogen ion concentration could result in depression of the respiratory centre with resultant apnoea particularly if the child has been hyperventilated during anaesthesia. Conn[7] reported an incidence of postoperative apnoea of 0·9 per cent in a series of 441 patients and Kumar and Bailey[5] an incidence of 2·7 per cent in 332 patients.

Although only 15 per cent of the patients who were alkalaemic on admission in our study were hypokalaemic as assessed by plasma potassium concentrations of less than 3 5 mmol/l, this is probably an underestimate of the true situation since many of the patients had capillary blood sampling in which higher potassium concentrations than in venous blood might be expected.

Plasma potassium is not a reliable indicator of total body potassium and potassium depletion and alkalaemia tend to coexist and aggravate each other[3,8]. When potassium depletion coexists with alkalaemia, sodium reabsorption across the distal renal tubules in exchange for hydrogen ions occurs in preference to potassium ions, thereby creating a situation of paradoxical aciduria in the face of alkalaemia. Although Howe and Le Quesne[9] state that potassium deficiency is not the prime cause of extracellular alkalaemia in pyloric stenosis and that administration of potassium will not by itself correct it, they recognized that the potassium deficiency does exacerbate the alkalaemia. Administration of sodium chloride is the mainstay of therapy, but potassium must also be given in severe cases to fully correct the disturbance. In their study of 14 patients, potassium was administered to every case (a mean of 258 mEq of potassium (range 130–407 mEq)). Correction of potassium depletion is, therefore, essential to achieve complete correction of alkalaemia.

Based on the result of a local survey in the West Midlands region, plasma chloride measurement is available in practically all clinical chemistry laboratories, although it is usually provided as a separate test on request and not part of a routine profile. The sample volume required varies from 20 μl to 200 μl depending on methodology.

In conclusion, plasma chloride is a reliable and valid parameter for the assessment and correction of hypochloraemic alkalaemia during resuscitation in infantile hypertrophic pyloric stenosis provided it is recognized that the concentration of plasma chloride at which adequate resuscitation and normoacidaemia is achieved is higher than previously accepted. We would recommend that an appropriate target plasma chloride concentration for resuscitation of these infants would be 106 mmol/l.

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Effect of branched chain amino acid enrichment of total parenteral nutrition on nitrogen sparing and clinical outcome of sepsis and trauma: a prospective randomized double blind trial

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Administration of extra branched chain amino acids (BCAA) has been associated with a nitrogen sparing effect in septic and traumatized patients. Whether nitrogen sparing is associated with decreased morbidity and mortality rates is unknown. We therefore undertook a prospective, randomized, double blind trial investigating the effects of BCAA enrichment of a total parenteral nutrition (TPN) regimen on nitrogen balance, 3-methylhistidine excretion, morbidity as evidenced by disturbances in organ function, severity of sepsis and mortality. One hundred and one patients entered the study; 52 received a standard TPN solution and 49 a BCAA-enriched solution. Both groups received 30 kcal kg^{-1} body-weight, 15 per cent fat calories and 0·17 g nitrogen kg^{-1} body-weight. In the BCAA-enriched group, patients received 0·56 g BCAA kg^{-1} body-weight (50·2 per cent BCAA). Standard group patients received 0·18 g BCAA kg^{-1} body-weight (15·6 per cent BCAA). Nitrogen balances and 3-methylhistidine excretion were not significantly different between groups. Although morbidity scores tended to decrease during the study, no difference was observed between groups. Mortality (early or late), sepsis or stress-related, did not differ significantly between groups. We were not able to confirm the reported beneficial effects of BCAA-enriched TPN solutions for use in septic and traumatized patients.

Keywords: Branched chain amino acids, total parenteral nutrition, sepsis, trauma

In an effort to reduce catabolism and loss of body mass during sepsis or after severe injury, a parenteral nutrition regimen has been advocated in which the amino acid component consists of 45–50 per cent of branched chain amino acids (BCAA), compared with 15–20 per cent in conventional regimens.

Transamination of BCAA occurs chiefly at extrahepatic sites because transaminase activity in the liver is low[1]. The resulting branched chain keto acids (BCKA) are released into the circulation only in very limited quantities. They are irreversibly degraded by BCKA dehydrogenase, a rate-limiting enzyme in the breakdown of BCAA chiefly located in liver, muscle, adipose tissue, kidney and brain. As a result, BCAA are degraded largely in muscle and adipose tissue. Because BCKA dehydrogenase activity in muscle is regulated by the energy charge and the energy charge has been reported to be low[2–4], BCAA degradation may be enhanced during severe sepsis and trauma. BCAA enrichment may also improve the precursor amino acid pattern for hepatic protein synthesis which is characterized during severe sepsis by decreased plasma BCAA levels and increased aromatic amino acid levels (AAA)[5]. *In vitro* studies demonstrate that BCAA, especially leucine, promote protein synthesis and BCKA inhibit protein degradation[6]. These reasons may provide a rationale for BCAA enrichment of total parenteral nutrition (TPN) solutions.

Several clinical studies have examined the effects of BCAA enrichment of TPN solutions in sepsis and trauma[7–13] but most were small without accurate patient descriptions. No studies have established a possible beneficial effect on morbidity and mortality rates in addition to the study for nitrogen sparing or effects on plasma proteins. We have therefore undertaken a prospective, randomized, double blind trial in septic and traumatized patients to confirm the nitrogen sparing effects of the BCAA enrichment and to establish the effects of such enrichment on outcome, measured through morbidity and mortality rates. The study was reviewed and approved by the Human Studies Committee of the University Hospital, Maastricht.

Patients and methods

Patients

Septic and metabolically stressed patients were eligible to enter the study. Sepsis was defined as the presence of a combination of the following criteria: spiking temperature, hyperventilation, tachycardia, elevated white blood cell count, decreased blood pressure, diminished urine output and positive blood cultures A clinically manifest septic focus and signs of septic shock were considered obligatory Patients were considered metabolically stressed if they had suffered multiple trauma, undergone operation for ruptured abdominal aortic aneurysm, severe non-septic pancreatitis, major gastrointestinal surgery or non-septic enterocolitis. Because it may be argued that under conditions without significant metabolic stress the presumed need for additional BCAA is absent and that in extremely ill patients no reasonably stable study conditions may be reached, patients suffering stress ranging from 20 to 50 per cent according to the criteria of Kinney *et al.*[14] were considered moderately stressed and analysed as a separate group

Study design

Patients were stratified for the presence of sepsis or stress and for age (under or over 65 years). They were randomized through the hospital

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Table 1 *Amino acid content per litre of the study solutions*

	BCAA (g)	Standard (g)
Essential amino acids		
L-leucine	6·10	1·80
L-phenylalanine	1·25	1·80
L-methionine	1·20	1·70
L-lysine hydrochloride	1·50	2·10
L-isoleucine	5·90	1·40
L-valine	5·30	1·30
L-histidine	0·90	1·30
L-threonine	0·80	1·20
L-tryptophan	0·40	0·50
Non-essential amino acids		
L-alanine	4·20	6·10
L-glycine	4·20	6·10
L-arginine	2·10	3·10
L-proline	0·80	1·20
L-tyrosine	0·08	0·12
Total amino acids	34·70	29·70
Total nitrogen	5·01	4·98

BCAA, branched chain amino acids

Table 2 *Stress factors in traumatized patients*

	Percentage
Elective surgery, postoperative	5
Soft tissue trauma	10–15
Peritonitis	10–20
Fracture, long bone	20–25
Multisystem trauma	20–50
Mild infection	0–20
Moderate infection	20–40
Severe infection	40–60

pharmacy to receive a BCAA-enriched or a standard solution. Both solutions were delivered to the ward labelled 'BCAA study solution' to ensure a double blind study design.

If renal failure progressed to a level necessitating protein restriction or dialysis, and if fluid restriction prohibited the use of the study solution, patients were withdrawn. The study was limited to 7 days. Each day, starting on day 0, 24 h urine was collected for nitrogen and 3-methylhistidine determination. Bistrian catabolic indices[15], Elebute and Stoner sepsis scores[16] and nitrogen balances were calculated daily. Mortality was recorded as early sepsis-related if death in overwhelming sepsis occurred within the 7-day study period, late sepsis-related if death occurred under septic conditions after the study period, or not sepsis-related.

Solutions

Both amino acid–dextrose mixtures contained equal amounts of amino acid nitrogen l^{-1}, derived in the standard solution from a balanced synthetic amino acid solution (Synthamin 14®, Baxter Healthcare Corporation, Deerfield, Illinois, USA), and derived in the BCAA-enriched solution from a more concentrated balanced synthetic amino acid solution (Synthamin 17®) and a 4 per cent BCAA solution containing equimolar amounts of valine, isoleucine and leucine. The standard solution contained 15·6 per cent BCAA and the BCAA solution contained 50·2 per cent BCAA of total nitrogen (*Table 1*). Each mixture contained 20 per cent glucose. Both nutritional support solutions were composed according to the standards of today's practice, providing sufficient minerals, trace elements, vitamins and free fatty acids. Caloric intake was calculated to meet basal energy expenditure (Harris– Benedict) augmented with 10 per cent specific dynamic action of food and a stress percentage as suggested by Kinney, ranging from 10 to 60 per cent[14] (*Table 2*), resulting in sufficient caloric intake to cover actual total energy expenditure[17]. Patients were not allowed any additional food. Blood and blood products were administered as required.

Morbidity parameters

Organ function was assessed using the scoring method as proposed by Stevens[18]. The scoring method was adapted to fit local treatment policies, e.g. the use of ventilatory support would not always reflect the presence of respiratory insufficiency and scoring respiratory function was therefore adapted as summarized in *Table 3*. Similar adjustments were made for scoring renal (creatinine clearance with each patient as his or her own control instead of plasma creatinine levels) and circulatory function (grouping of the Stevens scores to compensate for the use of dopamine to improve tissue perfusion, rather than to treat hypotension). In each organ system high scores represent organ function impairment, while low scores indicate a more normal function. Because of our interest in organ function *per se* rather than an overall morbidity score, our adaptation of the scoring system would not need further validation than performed by Stevens.

Organ function scores were assessed on days 0, 4 and 7.

Laboratory determinations

Urinary 3-methylhistidine content was analysed after hydrolysis on an LKB automated amino acid analyser (LKB Biochrom Ltd., Cambridge, UK). Urinary nitrogen excretion was analysed using the Kjeldahl method. Nitrogen balances were estimated by subtracting urinary nitrogen plus a correction factor for faecal and insensible losses from total nitrogen intake. Furthermore, a correction for accumulation or loss of urea was carried out, assuming the distribution volume for urea to be 60 per cent of body-weight. Nitrogen in plasma and albumin was considered protein available for metabolic processing and was therefore accounted for in nitrogen balances.

Statistical considerations

It was estimated that a 30 per cent reduction of a −20 g cumulative nitrogen balance in 1 week with a standard deviation of 10 g would be significant. To demonstrate such a result with $\alpha=0{\cdot}05$ and $\beta=0{\cdot}1$, we calculated that approximately 45 patients per study arm were required[19].

Results were evaluated using one way analyses of variance. Organ function scoring was evaluated using χ^2 tests.

Table 3 *Organ function scores*

Respiratory function

0. No respiratory support.
1. Spontaneous breathing with oxygen enrichment up to 30 per cent.
2. Spontaneous breathing with oxygen enrichment over 30 per cent.
3. Mechanical ventilation with less than 35 per cent oxygen.
4. Mechanical ventilation with more than 35 per cent oxygen or positive end-expiratory respiration.

If the ratio of arterial partial oxygen pressure (kPa) over oxygen fraction of inspired air (per cent) was under 40 the support was considered insufficient and one point was added to the original score.

Circulatory function

0. No impaired circulatory function (stable blood pressure).
2. Moderate circulatory insufficiency (stable blood pressure with more than normal fluid support and/or dopamine/dobutamine administration).
4. Severe circulatory insufficiency (labile blood pressure, despite increasing fluid needs and/or increasing doses of dopamine/dobutamine).

Myocardial infarction was excluded from the scoring.

Renal function

Renal function was assessed using creatinine clearance and expressed as a percentage of predisease levels, that were derived from a nomogram that considers serum creatinine concentrations and weight, age and sex[24].

0. ⩾100 per cent
1 75–100 per cent.
2 30–75 per cent.
3. <30 per cent
4. Dialysis needed.

Hyperbilirubinaemia

Primary hepatobiliary disease was excluded. Five categories were defined as follows:

0. 0–17 μmol l^{-1}
1. 17–34 μmol l^{-1}
2. 34–68 μmol l^{-1}
3. 68–136 μmol l^{-1}
4. >136 μmol l^{-1}

Table 4 *Study population*

	Total group (*n*=101)		Moderately stressed group (*n*=73)	
	BCAA (*n*=49) x̄(s.e.m.)	Standard (*n*=52) x̄(s.e.m.)	BCAA (*n*=35) x̄(s.e m)	Standard (*n*=38) x̄(s.e.m.)
Sex: female	21	25	14	19
male	28	27	21	19
Age (years)	56(2)	58(2)	59(2)	57(3)
BEE (kcal day^{-1})	1440(40)	1390(30)	1400(41)	1390(31)
Stress: 0–20%	5	4	–	–
20–50%	35	38	–	–
>50%	9	10	–	–
Elebute and Stoner sepsis score (day 0)	11·1(0·8)	10·9(0·9)	11·0(0·9)	10·0(0·8)
Bistrian score (day 0)	10·3(1·3)	9·8(1·0)	8·1(0·9)	9·8(0·9)

BCAA, branched chain amino acids; BEE, basal energy expenditure

Table 5 *Diagnoses*

	Total group (*n*=101)		Moderately stressed group (*n*=73)	
	BCAA	Standard	BCAA	Standard
Perforated viscera, anastomotic leakage, etc.	9	15	7	11
Pancreatitis	8	11	7	8
Enterocolitis (radiation, Crohn's disease, ulcerative colitis, ischaemia)	7	6	4	5
Intra-abdominal abscess	9	6	7	5
Multiple injuries	4	2	2	1
Ruptured aortic aneurysm	3	2	2	1
Other	9	10	6	7
Total	49	52	35	38

BCAA, branched chain amino acids

Results

Patients

One hundred and one patients were included in the study, with 61 of them requiring treatment in the intensive care unit. Forty-nine patients received the BCAA solution, and 52 the standard solution. Both groups were comparable for age and sex, calculated basal energy expenditure values on day 0, day 0 sepsis scores and catabolic indices (*Table 4*). Primary diagnoses were reasonably equally distributed (*Table 5*). Diagnoses listed under 'other' included tetanus, sepsis of unknown origin, respiratory insufficiency with pneumonia and prolonged paralytic ileus. The subgroup of moderately stressed patients (stress factor ranging between 20 and 50 per cent) was the largest in size and more homogeneous, because the more severely stressed group contained extremely ill patients, some of whom underwent one or more operations. Study groups within this moderately stressed population were also comparable with respect to all of the above criteria (*Tables 4* and *5*).

Solutions

Patients in both study groups received a similar nutritional support regimen, except for the BCAA content: 0·09 g BCAA nitrogen (0·56 g BCAA protein) *versus* 0·03 g BCAA nitrogen (0·18 g BCAA protein) kg^{-1} body-weight (*Table 6*).

Catabolic indices

Mean catabolic index scores in both groups decreased during the study without statistically significant differences between groups (*Figure 1*).

Sepsis scores

Mean sepsis scores remained in the same range in the branched chain group and tended to decrease in the standard group, but without a statistically significant difference between groups (*Figure 2*).

Morbidity scores

Results of organ function scoring are depicted in *Figure 3*. With the frequency of each score being expressed as a percentage of the total number of patients per study group, improvement of organ function was observed within each organ system, without difference between study groups. For statistical considerations changes of each organ function score were pooled per study group as increasing, stable or decreasing in the 0–4-day and 4–7-day periods and subsequently evaluated by a χ^2 test. No significant difference within any organ system was observed between groups.

Biochemical data

Figure 4 displays mean daily nitrogen balances corrected for urea accumulation per study group. The number of available

Table 6 *Total parenteral nutrition*

	Total group (*n*=101)		Moderately stressed group (*n*=73)	
	BCAA x̄(s.d)	Standard x̄(s.d.)	BCAA x̄(s d)	Standard x̄(s.d.)
NPE (kcal g^{-1} N)	205(33)	214(28)	202(24)	214(28)
NPE (kcal kg^{-1})	33(11)	34(9)	34(12)	34(9)
Nitrogen (g kg^{-1})	0·17(0·05)	0·17(0·04)	0·17(0·04)	0·17(0·04)
BCAA (g N kg^{-1})	0·09	0·03	0·09	0·03
Fat (%)	13(9)	16(8)	13(9)	16(8)
BEE (%)	148(35)	157(4)	152(36)	155(3)

BCAA, branched chain amino acids, NPE, non-protein energy; N, nitrogen; BEE, basal energy expenditure

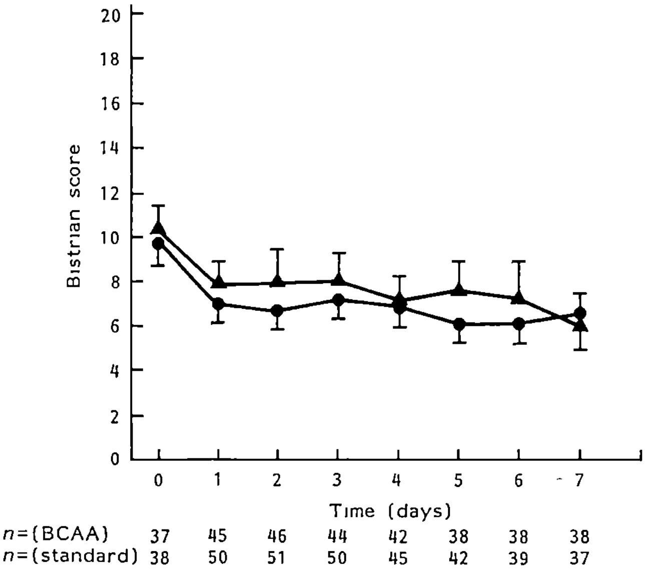

Figure 1 *Catabolic indices (mean(s.e.m.)) calculated according to Bistrian's method· ▲—▲, branched chain amino acids (BCAA), ●—●, control*

analyses is displayed, as in all other figures. Plasma protein-derived nitrogen intake was not different between study groups. Although in the total study population days 4 and 7 show a significantly ($P < 0{\cdot}05$, analysis of variance) less negative nitrogen balance in the BCAA group as compared with the standard group, cumulative 7-day nitrogen balances are not significantly different between groups (*Table 7*). Nitrogen balances in the moderately stressed patient group were consistently, albeit not significantly, less negative in the BCAA group (*Figure 5*). Cumulative nitrogen balances were less negative in the BCAA group but significance was not reached ($P = 0{\cdot}06$) (*Table 7*). Mean daily urinary 3-methylhistidine

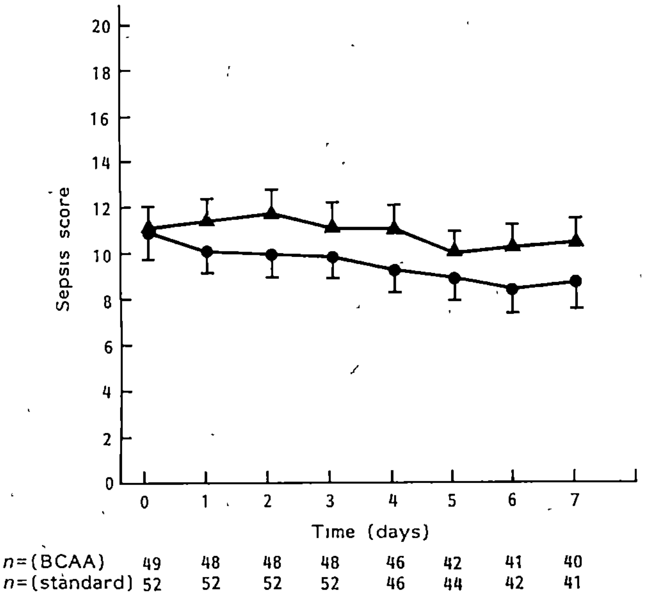

Figure 2 *Sepsis scores (mean(s.e.m.)) calculated as described by Elebute and Stoner.* ▲—▲, *branched chain amino acids (BCAA),* ●—●, *control*

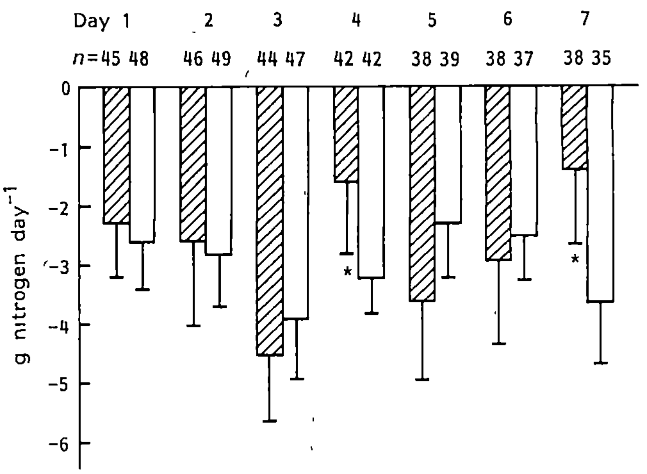

Figure 4 *Mean daily nitrogen balances in branched chain amino acids (BCAA) (▨) and control (☐) groups. Nitrogen balances are corrected for urea accumulation or loss, excessive stool, stoma or fistula output, and administration of plasma proteins.* * P<0·05

Table 7 *Cumulative 7-day nitrogen balance*

	Total group		Moderately stressed group	
	n	x̄(s.e.m.) (g)	*n*	x̄(s.e.m.) (g)
BCAA	37	−19·1(7·3)	28	−8·5(5·2)*
Standard	34	−20·8(4·5)	26	−23·0(5·5)

BCAA, branched chain amino acids; $^*P = 0{\cdot}06$ *versus* standard solution, moderately stressed group

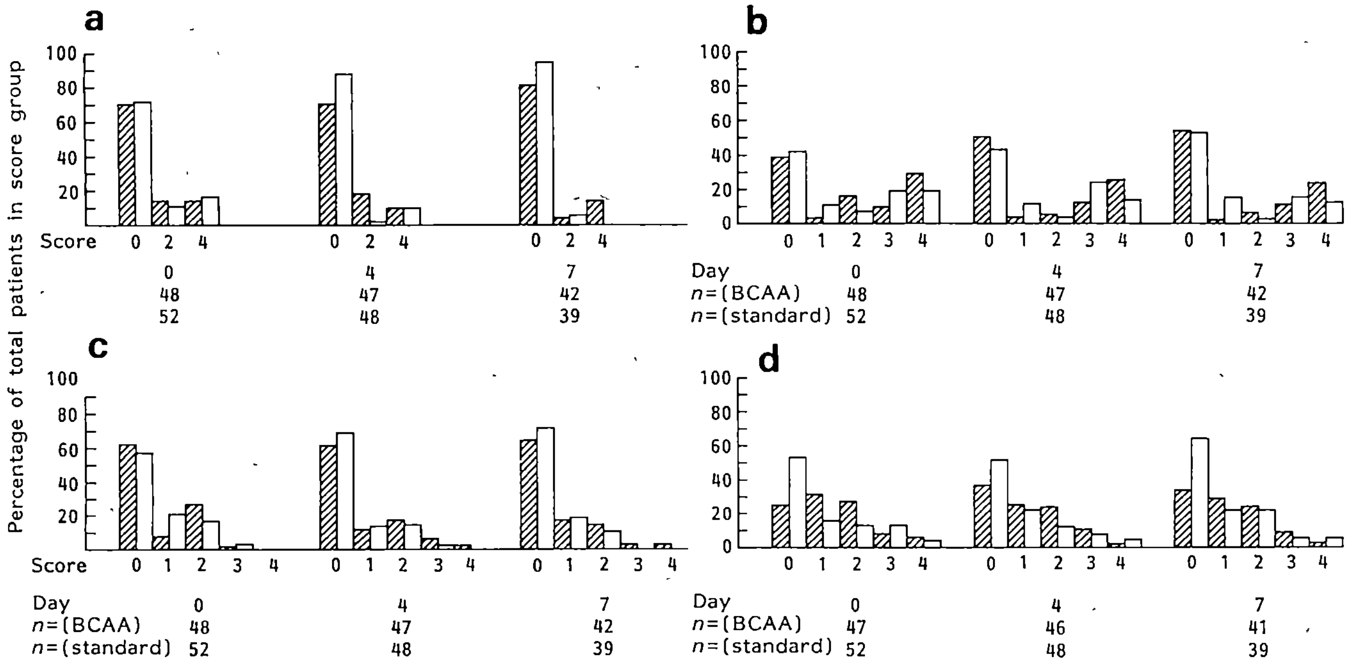

Figure 3 *Results of organ function scoring in branched chain amino acids (BCAA) (▨) and standard (☐) groups:* **a** *circulatory function. the number of low scores increases across days. Although high scores seem to diminish more in the standard group, a convincing advantage for the standard solution is not seen,* **b** *respiratory function: the number of 0 scores increases across days in both groups while higher scores decrease. No obvious difference between study groups is noticeable;* **c** *renal function. frequency of scores distribution does not seem to change across days in either solution:* **d** *liver function: distribution of scores for hyperbilirubinaemia was not equal in the study groups on day 0, with patients in the standard group showing score 0 significantly more frequently. A tendency towards improved organ function is noticeable without obvious advantage for either solution*

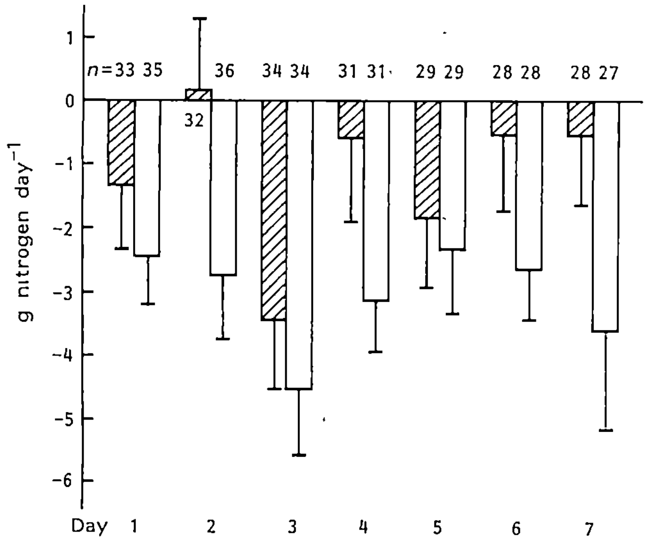

Figure 5 *Mean daily nitrogen balances in branched chain amino acids (BCAA) (▨) and control (☐) groups in the moderately stressed patient population*

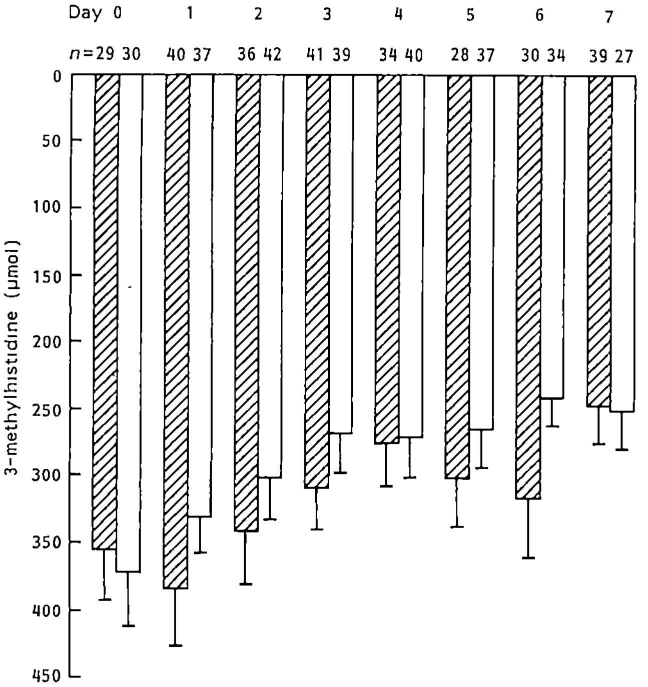

Figure 6 *Mean daily urinary 3-methylhistidine excretion in branched chain amino acids (BCAA) (▨) and control (☐) groups*

excretion diminished significantly during the study period, but no significant differences between groups were noted (*Figure 6*).

Mortality

Overall mortality rate was not different between groups (*Table 8*), nor was late or early sepsis-related mortality rate or non-sepsis-related mortality rate. Mortality rate was not different between groups in the moderately stressed study population either.

Discussion

The observation that nitrogen losses during sepsis and trauma can be diminished but not reversed with nutritional regimens of conventional composition, stimulated the development of special amino acid compositions. Specifically enrichment with BCAA may correct decreased plasma BCAA levels reported during sepsis and trauma, and consequently improve the precursor pattern for protein synthesis[20,21]. BCAA may further furnish fuel and promote protein synthesis[6].

Only two prospective randomized trials have been published investigating the effect of BCAA enrichment of TPN solutions in sufficiently large study populations[11,12]. In one trial patients with pancreatitis and organ failure were excluded[11] An improvement of nitrogen balance was found only on the fourth day of the 7-day study period. In the other trial, patients suffering a uniform trauma were studied in a multicentre study design[12]. Patients were dropped from the study once the development of organ failure became apparent. As in the previous study a modest though not statistically significant improvement of nitrogen balance was observed in one of the trial subgroups. In these studies the clinical state of the patients was not detailed before, during or after the study period, nor was this done in either of the other smaller studies[7–10,13].

We tried in this trial to demonstrate an improved nitrogen balance and clinical benefit in an unselected study population suffering from severe illness or sepsis. The assessment of clinical performance of each individual organ system must be the most accurate and independently obtainable measure to study clinical efficacy. To detect differences larger patient groups were necessary which were comparable in every respect We therefore stratified for age, sepsis and stress and ensured that patients received an amount of calories equalling their estimated actual energy expenditure. All patients received fat, and no patient received more than 35 carbohydrate calories kg^{-1} 24 h^{-1}. Patients received on average 1·1 g AA kg^{-1} 24 h^{-1} and 0·56 g BCAA kg^{-1} 24 h^{-1} in the enriched group which is in the range where an eventual benefit on nitrogen balance should have manifested itself[22]. If patients were considered more severely stressed they received proportionally more calories and nitrogen, including BCAA. Both groups (controls and BCAA-enriched) proved to be comparable at day 0 with regard to disease, age, sex, sepsis scores, Bistrian score and organ function score. Only hyperbilirubinaemia was encountered more often in the BCAA-enriched group.

We are aware that the methods used to estimate nitrogen balances include crude approximations but few studies have made an attempt to correct for total body urea accumulation or the metabolic fate of exogenous protein[23].

The study failed to confirm a clear benefit of BCAA enrichment on nitrogen balance in the total patient population. When the subgroup that was considered moderately stressed on day 0 was selected ($n=73$), cumulative nitrogen balance improved in the BCAA-enriched group although this improvement failed to reach significance ($P=0·06$). In this group nitrogen balance was better on any single day (days 1–7) although on no occasion was significance reached.

BCAA enrichment may improve nitrogen balance in moderately stressed patients but differences in clinical outcome (mortality, organ function, catabolic indices and sepsis score) were not observed. The results of this trial may be explained by the fact that clinical outcome in septic or traumatized patients is much more dependent on the success of primary treatment (drainage of abscesses, debridement of necrotic tissue,

Table 8 *Mortality*

	Total group		Moderately stressed group	
	BCAA ($n=49$)	Standard ($n=52$)	BCAA ($n=35$)	Standard ($n=38$)
Early sepsis-related	4 (8·2)	2 (3·8)	2 (5·7)	2 (5·3)
Late sepsis-related	8 (16·3)	10 (19·2)	7 (20·0)	3 (7·9)
Not sepsis-related	5 (10·2)	4 (7·7)	5 (14·3)	3 (7·9)
Total	17 (34·7)	16 (30·7)	14 (40·0)	8 (21·1)

Values in parentheses are percentages. BCAA, branched chain amino acids stabilization of fractures, etc.) than on supportive care. The acute effects of nutritional support, let alone the effects of a modification of nutritional support under such conditions, must be limited. We conclude that BCAA-enriched TPN solutions, commonly marketed as 'trauma solutions', possibly achieve a modest improvement in nitrogen balance in moderately stressed patients but do not induce a clear clinical benefit.

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Which balloon embolectomy catheter?

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This study compared seven makes of balloon embolectomy catheter currently available, testing the most commonly used 4 Fr catheters. The volume of fluid and inflation pressure required to burst balloons of each type were measured. All balloons showed a similar shape of inflation curve, but compliance varied considerably, and the pressure required to burst different balloon types varied from 1060 to 1920 cmH$_2$O. Two balloon types consistently fragmented when they burst in free space. On a specially designed mechanical rig balloon catheters were pulled through a 6 mm tube containing a fixed stenosis, with continuous measurement of traction force and intraballoon pressure. Traction force varied from 34 to 129 g (median 40 g) during passage along the tube, and from 254 to 463 g (median 350 g) during passage through the stenosis. The shear force imparted by the balloon to the tube wall was also calculated. This study provides comparative data which may help to guide surgeons in their choice of balloon embolectomy catheter.

Keywords: Arterial occlusive disease, arteries, embolectomy catheter, embolism (blood), thrombosis

Balloon embolectomy catheters were introduced by Fogarty and colleagues[1] in 1963, and their use in removing thrombus from arteries is well established. Recently several new catheters have appeared on the market but few data exist to guide the surgeon in his or her choice

This study provides comparative information on seven commercially available embolectomy catheters tested in a series of *in vitro* experiments.

Materials and methods

Size 4 Fr balloon catheters were evaluated since these are the most commonly used in surgical practice Two sets of experiments were performed. In both, balloons were primed with distilled water and exercised according to the manufacturers' instructions. Attempts were made to remove air bubbles.

Balloon filling and bursting

Four balloon catheters of each make were studied The primed catheter was connected to a minimally compliant water-filled pressure transducer and a preprimed 5 ml plastic syringe accommodated in a modified infusion pump. The pressure-measuring system was designed to be linear up to 2000 cmH$_2$O, and regular calibration to 400 cmH$_2$O was performed with a mercury sphygmomanometer.

Intraballoon pressure (P), commencing at just below atmospheric, was continuously recorded as distilled water was infused into the balloon catheter at a constant rate of 0·48 ml/min. The time taken to burst after crossing zero pressure gave the balloon bursting volume (V_B), and the bursting pressure (P_B) was taken from the chart recording.

Assuming that the embolectomy catheter lumen, pressure measurement and infusion systems were minimally compliant compared with the balloon, then the duration of each inflation curve is directly proportional to the volume (V) of water infused into the balloon. Since compliance (C) is defined by·

$$C = \Delta V / \Delta P$$

the tangent to the inflation curve at any given volume represents the balloon compliance at that volume.

During the inflation routine, the balloon section of the catheter was freely suspended inside a glass jar to facilitate collection of any fragmented material on balloon disruption. Some bursting trials were recorded on video for further analysis

Withdrawing balloon catheters through a tube

An electromechanical rig was developed to pull a fluid-inflated balloon catheter at a constant velocity through a polythene tube with a stenosis whilst continuously recording intraballoon pressure and withdrawal force (*Figure 1*).

Transparent polythene tubing of 6 mm internal diameter (d) was used and the stenosis was created by compressing the tube to half its external diameter in one axis using a screw clamp. Before testing each catheter the lumen of the tube was lubricated consistently by pulling through a bolus of KY jelly® (Johnson and Johnson Limited, Slough, UK) using an embolectomy balloon catheter inflated to a fixed volume.

Each balloon catheter was inserted to a fixed point in the polythene tube distal to the stenosis. A 1 ml syringe was used to inflate the balloon to a mean pressure of 1000 cmH$_2$O and a tap closed to maintain constant fluid volume in the embolectomy catheter and pressure measuring system. The proximal end of the catheter was clamped to a low friction trolley connected via a force transducer to a motorized constant velocity puller.

The average axial length (L) of surface contact between the balloon and tubing lumen was measured using calipers, allowing estimation of surface contact area (A):

$$A = \pi d L$$

The embolectomy catheter was pulled at constant velocity along the tube and through the stenosis. Three balloon catheters of each make were studied. Each catheter underwent three withdrawal procedures, providing nine sets of force and pressure curves for each make of catheter. In addition the force (F_t) required to pull the trolley alone was recorded between each new catheter trial. This unwanted component of the force measured during catheter withdrawal was subtracted when the chart recordings were analysed, to provide an estimate of the force (F) required to pull the balloon catheter alone.

The surface area of contact (A) was assumed not to change significantly as the balloon was drawn along the prestenotic section of the tube and so the shear stress (S) imparted by the balloon on the tube was estimated from·

$$S = F / A$$

Statistical evaluation

For each of the variables measured all balloon makes were compared for statistical significance between mean values. The comparison was made, assuming normal distributions, by computing the standard error of the difference between sample means and mean difference.

Since the number of measurements conducted on each catheter make was relatively small, statistically significant differences are only quoted when $P \leqslant 0.001$.

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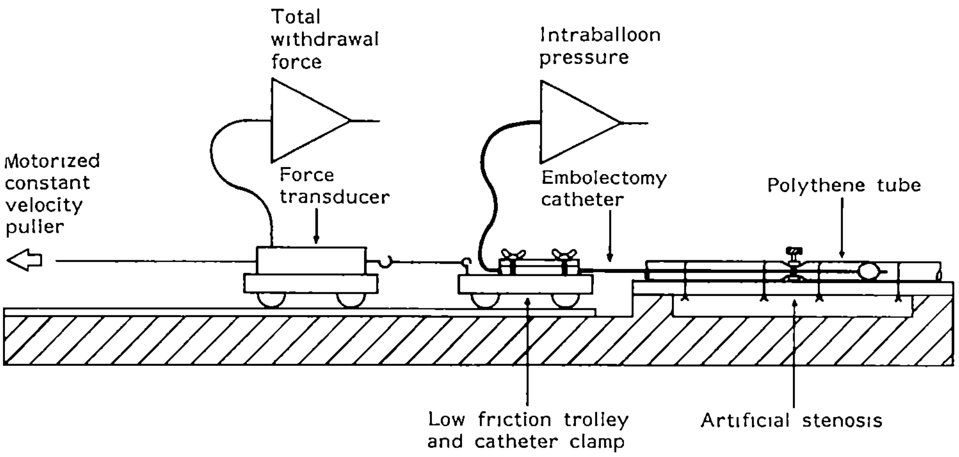

Figure 1 *The electromechanical rig to pull a fluid-inflated balloon catheter at a constant velocity through a polythene tube with a stenosis whilst continuously recording intraballoon pressure and withdrawal force*

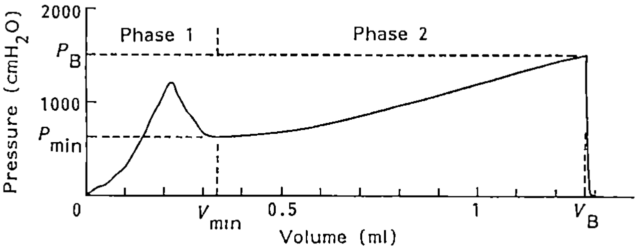

Figure 2 *Balloon filling in free space The plot of pressure against volume shows two phases – the first as the balloon forms its natural filled shape when a fall in pressure occurs, and the second a gradual rise in pressure until the balloon bursts*

Table 1 *Manufacturers' recommended inflation volumes (MRIV) together with mean(s d.) values for balloon bursting pressure* (P_B) *and bursting volume* (V_B) *and the pressure and volume values* (P_{min} *and* V_{min} *respectively) at which balloon compliance changes from negative to positive*

Catheter type	MRIV (ml)	V_{min} (ml)	V_B (ml)	P_{min} (cmH_2O)	P_B (cmH_2O)
Bard Parker	0·45	0·23(0·03)	1·14(0·11)	398(71)	1275(119)
Cabot	0·75	0·27(0·05)	1·34(0·11)	613(36)	1475(67)
Fogarty	0·75	0·31(0·05)	1·78(0·15)	620(46)	1835(55)
Eschmann	0·50	0·31(0·03)	1·90(0·07)	700(45)	1693(93)
Impra	0·75	0·33(0·06)	1·67(0·21)	663(73)	1493(152)
Shiley	0·35	0·37(0·04)	2·33(0·04)	553(29)	1290(46)
Meadox	0·75	0·43(0·03)	3·32(0·59)	444(70)	1212(137)

Results

Balloon filling and bursting

All 28 balloon inflation curves demonstrated the same basic profile (*Figure 2*). As filling commenced, a rapid rise in balloon pressure occurred (phase 1) to a point of peak pressure which corresponded to the balloon attaining its natural filled shape. The balloons then accommodated a further small amount of fluid with an actual decrease in pressure (negative compliance) to a minimum value (P_{min}) at a balloon volume (V_{min}). This was followed by a steady though a more gradual rise in pressure as the balloon continued to fill (phase 2), but with a higher compliance, and eventually balloon bursting occurred.

Mean values and standard deviations for P_{min}, V_{min}, P_B and V_B are listed in *Table 1* for each of the seven catheter types. In addition, the manufacturers' maximum recommended inflation volumes with water are shown.

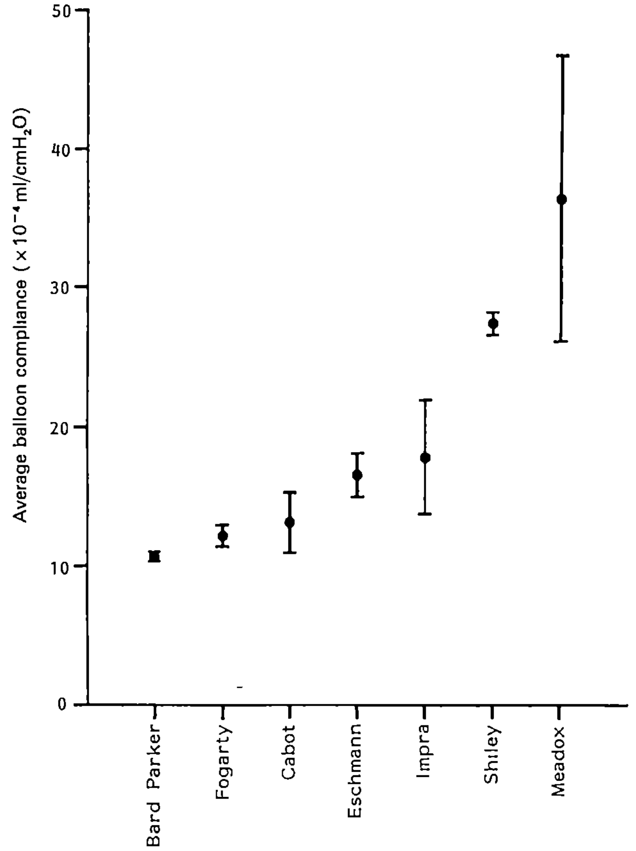

Figure 3 *Average balloon compliance (mean and standard deviation) for each catheter type*

With the exception of the Shiley catheter, the volume, V_{min}, was always less than the maximum recommended inflation volume. Consequently, inflating the balloons to or just below the maximum recommended inflation volumes corresponded to a phase 2 characteristic (*Figure 2*) and hence an average balloon compliance, C_2, for this region was defined as:

$$C_2 = (V_B - V_{min})/(P_B - P_{min})$$

Figure 3 presents the mean and standard deviation values for compliance in the seven catheters.

The results of balloon bursting in free space are shown as part of *Figure 7*. There were important differences in the tendency of balloons to fragment, and two balloon types did so on all four occasions of testing.

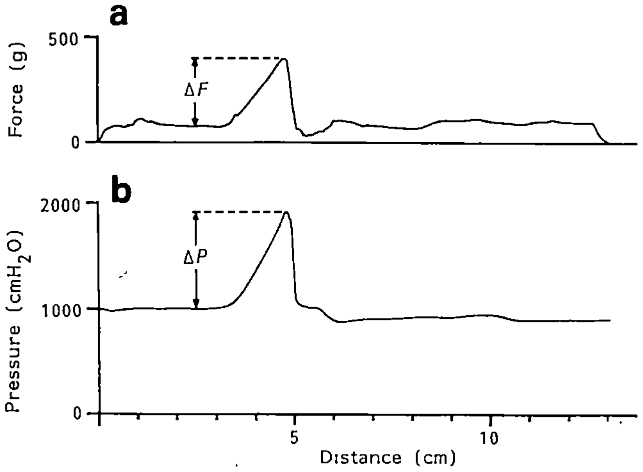

Figure 4 *Pulling the inflated balloon along the tube and through the stenosis;* **a** *shows changes in traction force and* **b** *shows changes in balloon pressure, both of which rise to a peak on passage through the stenosis*

Table 2 *Mean(s.d.) values for the length of surface contact between balloon and tubing lumen* (L), *surface contact area* (A) *and traction force to withdraw the balloon through the constant cross-section segment of the polythene tube* ($F_{plateau}$)

Catheter type	L (mm)	A (cm^2)	$F_{plateau}$ (g)
Fogarty	9·7(0·7)	1·82(0·13)	34·4(10·7)
Impra	7·4(0·7)	1·39(0·13)	34 4(11·7)
Eschmann	7 9(1 2)	1·48(0·23)	38·9(12 9)
Bard Parker	8·4(0·5)	1·58(0 09)	40·0(25·8)
Cabot	9·7(1·3)	1·82(0·25)	41 1(8 1)
Shiley	10·6(1 2)	1·99(0 22)	50·0(8·2)
Meadox	19·0(1 6)	3·58(0·31)	128 9(63·1)

Withdrawing balloon catheters through a tube

All balloon withdrawal experiments showed force and pressure curves with similar profiles (*Figure 4*). During balloon withdrawal through the constant cross-section segment of the polythene tube, the horizontal force to pull the catheter and intraballoon pressure remained relatively constant. Mean traction forces ($F_{plateau}$) were in the range 34–129 g, and pressure remained at or near the initial priming value of 1000 cmH$_2$O When the inflated balloons negotiated the stenosis, both the force and pressure increased rapidly from their prestenotic plateau values, peaking as the balloon passed through the narrowing, with corresponding maximum increases in force and pressure of ΔF and ΔP respectively (*Figure 4*).

Mean values and standard deviations for the catheter withdrawal parameters, L, A and $F_{plateau}$, are listed in *Table 2*. The values of mean shear stress for each make of catheter are represented graphically in *Figure 5*. For the stenotic region a plot of ΔF against ΔP demonstrates the positive correlation between these two parameters (*Figure 6*).

Discussion

Arterial injury by balloon catheters is well recognized[2,3], and skilful use of these devices is essential, particularly in diseased vessels. It is interesting to examine whether the present data suggest that certain balloon types might be more likely to cause intimal damage because of their physical characteristics.

Meadox and Shiley balloons accommodated statistically significantly higher volumes before bursting than all the others. Not surprisingly, therefore, these catheters were also significantly the most compliant. By contrast, the Bard Parker catheter had significantly lower compliance than all the other

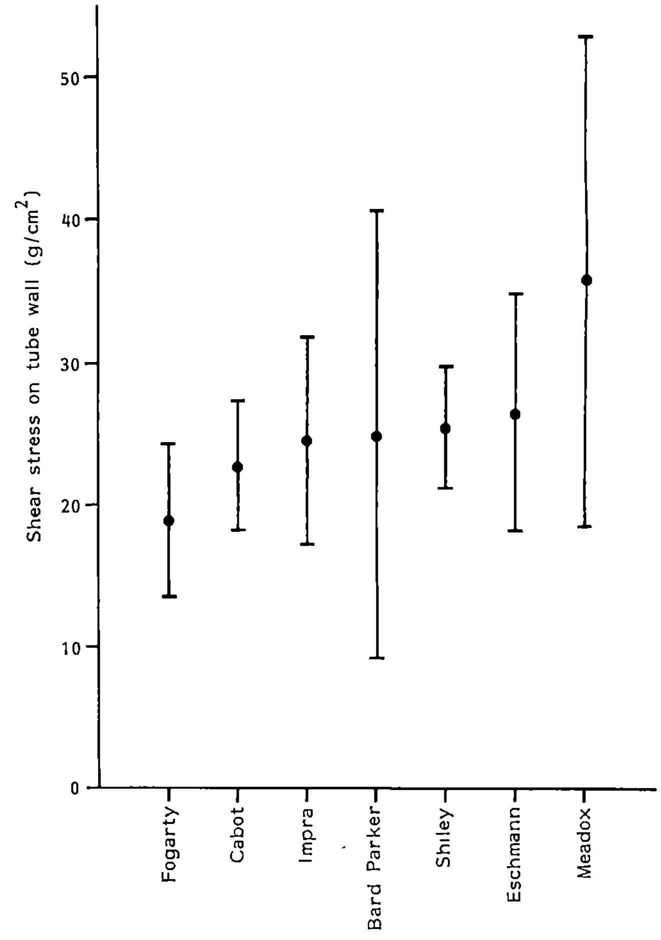

Figure 5 *Shear stress on the tube wall imparted by each balloon catheter type Mean values and standard deviations are shown*

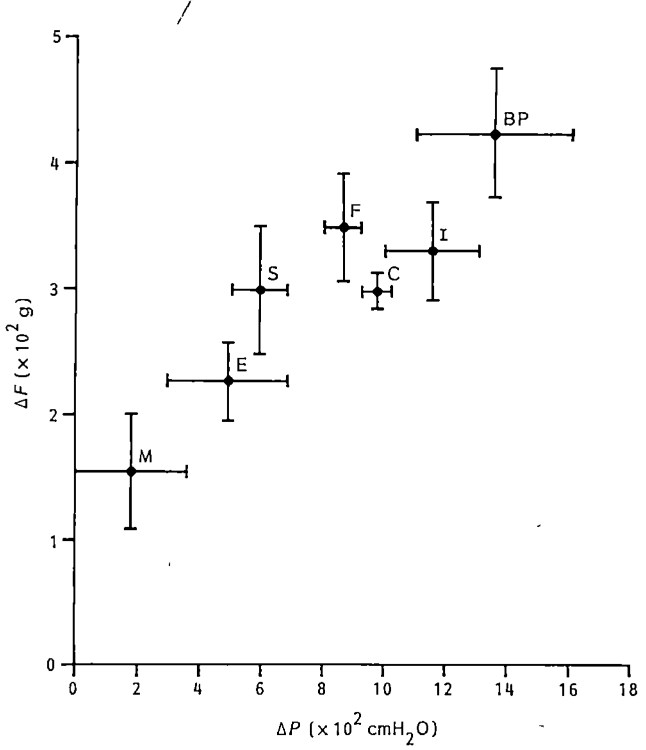

Figure 6 *A plot of maximum change in force against maximum change in pressure on passage through the stenosis for each balloon catheter type Mean values and standard deviations are shown M, Meadox; E, Eschmann; S, Shiley, F, Fogarty, C, Cabot, I, Impra, and BP, Bard Parker*

	Bursting volume	Bursting pressure	Compliance	Fragmentation	Shear stress	Change in force through stenosis	Change in pressure through stenosis	Catheter cost (£)
Bard Parker	■	☐	■	☒	☐	▤	▤	25.50
Cabot	◪	☐	☐	■	☐	☐	▨	20.00
Impra	☐	☐	☐	▲	☐	☐	▤	20.00
Fogarty	☐	▤	☐	■	☐	☐	☐	29.50
Eschmann	☐	▨	☐	▲	☐	■	◪	27.00
Shiley	▤	☐	▤	☒	☐	☐	◪	26.00
Meadox	▤	☐	▤	☒	☐	■	■	29.00

Figure 7 *A comparison of balloon characteristics and one-off costs (as of October 1989) indicating statistically significant differences* (P$\leqslant$*0 001) between makes* ▤, *significantly higher than in at least five other makes,* ▨, *significantly higher than in at least four other makes;* ☐, *significantly different to at least three other makes;* ◪, *significantly lower than in at least four other makes;* ■, *significantly lower than in at least five other makes;* ▲, *one balloon fragmentation*

types apart from Cabot. There are theoretical advantages and disadvantages of high or low volume and compliance, and it is difficult to be dogmatic about which is 'better'. A compliant balloon causes less arterial distortion, but a predictable small size of balloon also has advantages because high intraballoon pressure does not necessarily transmit to the arterial wall, provided the balloon is of similar size to the arterial lumen[4], and its area of wall contact may be small.

High compliance probably contributed to significantly lower changes in force and pressure through the stenosis for the Meadox balloon but this was not so for the Shiley. Unexpectedly the Eschmann also demonstrated significantly lower changes in force and pressure.

It was initially thought that the significant differences in balloon parameters would be reflected in differences of shear stress during withdrawal through the tube, but this was not the case. No statistical differences were noted between any balloons with respect to shear stress. This is an important observation, because the histological injury to arterial intima and subsequent myointimal hyperplasia have been related to the shear forces involved[5–7]. In this respect no balloon has a significant disadvantage.

The way in which these observations might influence a surgeon's choice of balloon catheter will be determined to some extent by personal preference The surgeon who likes a firm, direct 'feel' from a balloon catheter is likely to choose a low volume, less compliant balloon. Other features, such as novel balloon shapes, provision of a catheter lumen for distal infusions, and extra flexibility of catheter tips, may also influence choice.

In order to highlight some of the differences demonstrated, we have constructed a table similar to that used by the Association for Consumer Research in their *Which?* magazine comparisons (*Figure* 7). Note that the degree of shading of the comparison squares cannot necessarily be equated with 'better' or 'worse' features. The table, however, does allow easy comparison of the differences in balloon characteristics, together with cost information

This study suggests that no balloon embolectomy catheter has major physical advantages or disadvantages over the others, but provides data which may help the individual surgeon in his or her choice

Acknowledgements

The authors thank Dr E D James for his advice during the preparation of this work, and are also grateful to the manufacturers for their co-operation in supplying the balloon catheters used in this study· Shiley, Shiley Ltd., Windsor, UK; Bard-Parker, Becton-Dickinson UK Ltd., Oxford, UK, Cabot, Cabot Ltd , High Wycombe, UK, Eschmann, Eschmann Heathcare, Lancing, UK, Meadox, Meadox (UK) Ltd., Dunstable, UK; Fogarty, Baxter Health Care Ltd., Newbury, UK; and Impra, Impra UK Ltd., Ascot, UK

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Reappraisal of the oxygenation of blood in varicose veins

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Raised oxygen tension in the blood of varicose veins has led to arteriovenous communications being implicated in the pathogenesis of varicose veins. The aim of this study was to compare the oxygen tension of blood from varicose veins with that from normal legs, and to observe the effect of posture on these measurements. Twenty-six subjects (13 normal controls and 13 with uncomplicated varicose veins) had blood sampled from the long saphenous vein or a varicose vein near the ankle. Samples were taken after 30 min in the supine position and repeated after 30 min standing. Samples were also taken simultaneously from the arm. Transcutaneous oxygen measurements of the gaiter skin were performed continuously throughout the experiment. In the supine position, blood from varicose veins had a significantly higher oxygen tension (median = 6·09 kPa) than that from normal veins (median = 4·54 kPa) (P = *0·022*). *In all subjects, there was a higher oxygen tension in leg vein blood when lying (varicose vein median value = 6·09 kPa, control median value = 4·54 kPa) than while standing (varicose vein median value = 3·93 kPa, control median value = 3·74 kPa)* (P < *0·002, varicose vein group;* P = *0·005, normal group). Changes in transcutaneous oxygen tension correlate poorly with changes in venous blood. It is concluded that the theory of arteriovenous anastomoses is only one among a number of possible explanations for the pathogenesis of varicose veins.*

Keywords: Varicose veins, oxygen tension, transcutaneous oxymetry

The pathogenesis of varicose veins is imperfectly understood. Current theories suggest that primary valve failure occurs in the long saphenous, short saphenous or perforating veins. This may be due to connective tissue disorders of the vein wall or humoral factors[1]. In 1843 Pigeaux observed that blood from varicose veins was sometimes as red as that from arteries[2]. This observation was pursued by Blalock who reported a higher oxygen content in varicose veins than in normal veins, and concluded that 'the total flow of blood through a leg with varicose veins is increased'[3]. These findings have been corroborated by later authors[4,5] and have been used as evidence for the presence of abnormal arteriovenous communications as a causative factor in varicose vein disease.

The purpose of this study was to compare the oxygen tension of blood from patients with varicose veins with that from normal veins in the leg and arm and to observe the effect of posture on the pressure of venous oxygen ($P_{\mathrm{v,O_2}}$) in these groups. A relationship between the changes in the transcutaneous oxygen ($P_{\mathrm{tc,O_2}}$) and the venous $P_{\mathrm{v,O_2}}$ with position was also examined.

Patients and methods

A total of 26 subjects were studied. Varicose veins were present in 13 patients and 13 were normal controls Patients with varicose veins were examined using duplex ultrasound to confirm the presence of superficial venous reflux; none had evidence of deep vein reflux. Control subjects were hospital inpatients being treated for other conditions, or were members of the Department of Surgery. Patients having conditions that might be expected to influence the $P_{\mathrm{v,O_2}}$ were excluded (e g patients with respiratory disease). The control group did not undergo duplex scanning, but were examined clinically to exclude the presence of asymptomatic varicose veins Any suggestion of the presence of abnormal veins, or a history of varicose veins in the past, resulted in exclusion from the control group.

The study was undertaken in an environmental chamber maintained at 22°C and 20 per cent relative humidity. Patients lay supine for 20 min and were allowed to acclimatize to the ambient conditions. An oxygen electrode (Kontron, Munich, FRG) was attached to the chest and the transcutaneous oxygen tension measured. The chart recording was interpreted when the electrode had equilibrated with the skin and the reading was steady. The electrode was then moved to the gaiter region 5 cm proximal to the medial malleolus, and the $P_{\mathrm{tc,O_2}}$ read when the chart recording had again reached a steady plateau. At the end of this period blood was taken from the cephalic vein and from a varicosity of the calf close to the medial malleolus using a 2 ml heparinized syringe and a 23 Fr gauge needle. In normal subjects blood was taken from the long saphenous vein 1–2 cm proximal to the medial malleolus. Subjects then stood for 30 min with their arms at their sides. Blood was taken from the arm and leg, as before. The $P_{\mathrm{tc,O_2}}$ was measured when the chart recording had attained a steady reading.

The venous oxygen tension ($P_{\mathrm{v,O_2}}$) was determined immediately after sampling by means of a Radiometer ABLL 300 gas analyser (Radiometer, Copenhagen, Denmark) which was in constant use. Mann–Whitney *U* and Wilcoxon signed rank tests were employed for statistical analysis of the data.

Results

The venous oxygen tension ($P_{\mathrm{v,O_2}}$) in blood taken from the leg was higher in the varicose vein group (median 6·09 kPa) than in control subjects (median value 4·54 kPa; $P = 0{\cdot}022$), after lying supine for 30 min (*Figure 1*). Blood taken from the arm showed similar oxygen tension in the two groups. In the supine position, both groups had a higher oxygen tension in the leg than in the arm blood. The median difference was 1·66 kPa in the varicose vein group, and 0·74 kPa in the normal group (*Figure 2*).

There was a fall in the leg $P_{\mathrm{v,O_2}}$ after 30 min standing in both control and varicose vein groups (*Figure 3*). A similar final value was obtained in both groups (varicose vein group median 4·01 kPa, normal group median 3 74 kPa; n.s.). The arm $P_{\mathrm{v,O_2}}$ remained unchanged in both groups and on standing there was no difference between leg and arm $P_{\mathrm{v,O_2}}$ measurements.

There was a rise in the $P_{\mathrm{tc,O_2}}$ in both groups after 30 min standing, with a median increase of 0·8 kPa in the varicose vein group and 0·93 kPa in the normal group (*Figure 4*).

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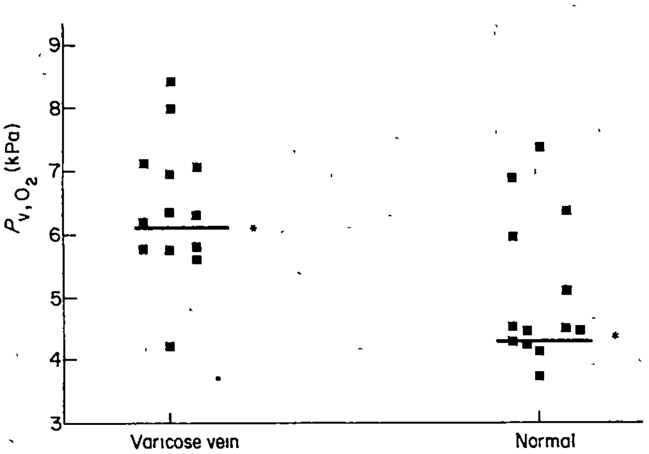

Figure 1 *Leg P_{v,O_2} values in the supine position in varicose vein patients and controls. Individual and median values are shown.* *P=0·022 (*Mann–Whitney* U *test*)

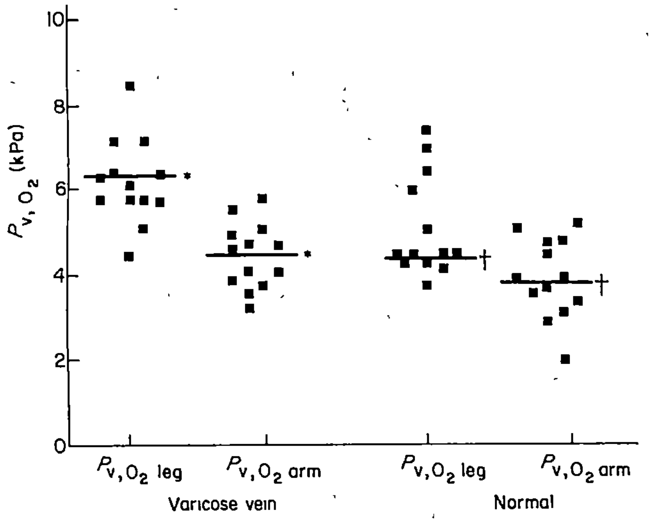

Figure 2 *Leg and arm P_{v,O_2} values in the supine position in varicose vein patients and controls. Individual and median values are shown.* *P=0·002, †P=0·017 (*Wilcoxon signed rank test*)

Discussion

In his original study, Blalock compared blood from varicose veins with that from normal veins in the unaffected limb, using a Van Slyke–Neill manometric blood gas analyser (which measures blood gas volume, not oxygen tension). Using a group of normal controls, we have confirmed his principal finding that the oxygen tension is higher in blood from varicose veins than in normal veins in the supine position. In addition, we have shown that, while supine, superficial venous blood in the leg has a higher oxygen content than that in the arm, whether varicose veins are present or not. This has not been reported previously. We have confirmed that venous oxygen tension in the leg falls on standing, in which position there is no significant difference between the groups.

Reikeras and Sorlie[6] found that the oxygen tension in blood from varicose veins was lower than that in blood from normal veins in the dependent position, although when they compared the differences between blood sampled from the deep veins this difference was not apparent. They failed to demonstrate a raised P_{v,O_2} in their patients with varicose veins, and this may be because all their samples were taken with the patient in the standing position.

Haimovici[7,8] has reviewed the evidence for the presence of arteriovenous communications in patients with varicose veins. Early venous filling during angiography, Doppler flow measurements[9] and direct visualization at operation[7,10,11] have led to the hypothesis that this may be the aetiological factor in most cases of varicose veins. Similarly, Piulachs and Vidal-Barraquer in 1953 attributed their findings of high P_{v,O_2} in varicose veins to these abnormal vessels and described their presence at operation[12]. However, more rigorous examination of the microcirculation using macroaggregates has failed to demonstrate increased arteriovenous shunting in patients with varicose veins[13].

Our findings are consistent with the presence of arteriovenous shunting, but could have other explanations. In particular, the fact that normal subjects while supine have a higher P_{v,O_2} in the lower than the upper limbs, suggests that a physiological rather than pathophysiological mechanism is at work. Different metabolic rates in the foot and the hand may explain the phenomenon. The ratio of red ('slow twitch') fibres to white ('fast twitch') fibres is greater in the postural muscles of the leg[14]; and as the two types of fibre have different metabolic rates[15] it is reasonable to expect different oxygen tensions in the venous blood draining them.

The postural change in P_{v,O_2} may be explained on purely physiological principles alone. It is well recognized that on rising from the supine to the standing position there is a fall in cardiac output of approximately 40 per cent[16]. It has been demonstrated that in normal subjects the blood flow to the

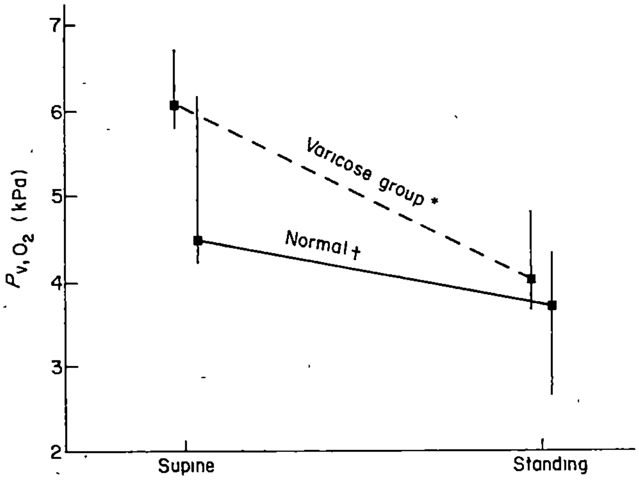

Figure 3 *Change of leg P_{v,O_2} when moving from the supine to standing position in varicose vein patients and controls. Median values and quartile ranges are shown.* *P=0·002, †P=0·005 (*Wilcoxon signed rank test*)

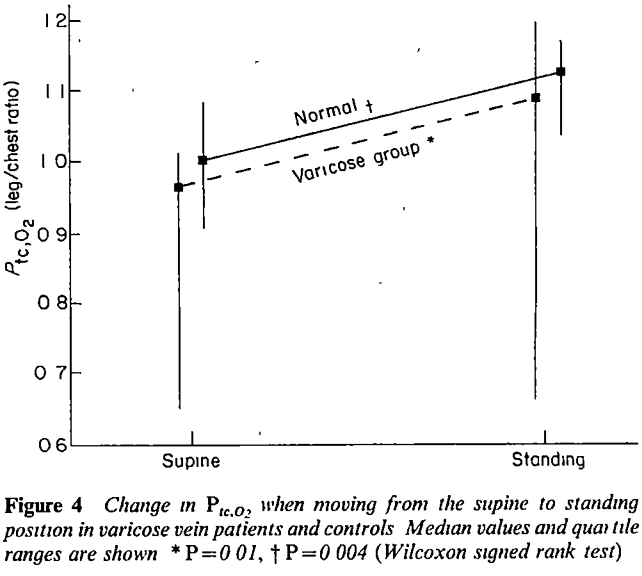

Figure 4 *Change in P_{tc,O_2} when moving from the supine to standing position in varicose vein patients and controls. Median values and quartile ranges are shown* *P=0·01, †P=0·004 (*Wilcoxon signed rank test*)

lower limb falls by between 40 and 60 per cent on rising from the lying to the standing position[17]. This reduced blood flow to the tissues would be expected to produce a fall in venous oxygen tension exactly as we have observed. The differences between venous oxygen tensions in the leg and arm at rest ideally need to be examined with the knowledge of the specific blood flow to both limbs under study. A simple explanation of the differences in venous oxygen tensions in the leg and arm veins in the supine position could be that the specific blood flow to the leg is higher than that in the arm under these conditions. This avoids the need to invoke the presence of abnormal arteriovenous communications. One other possibility is that the skin diffusion defect postulated in patients with venous insufficiency, as suggested by Browse and Burnand[18], or the perfusion defect proposed by Coleridge Smith *et al.*[19], might also be sufficient to result in elevation of the venous oxygen tension in subjects with varicose veins.

The rise in the transcutaneous oxygen tension observed when the patient rises from the lying to standing position can also be explained on simple physical principles alone. With a patient supine the pressure in the veins and capillaries of the lower limb will be equal to atmospheric pressure (normally 760 mmHg). On rising to the standing position this pressure will increase by between 80 and 100 mmHg in the veins and presumably the capillaries as well. This rise in absolute pressure will be reflected in an increase in the partial pressure of oxygen within the capillaries that will subsequently be measured by the transcutaneous oxygen electrode The predicted rise, approximately 12 per cent, is exactly that which has been observed in this study.

We have been unable to confirm the findings of Wyss *et al.*[20] who found a good correlation between $P_{\mathrm{tc,O_2}}$ and the underlying venous $P_{\mathrm{v,O_2}}$. In our study, there was a median rise in $P_{\mathrm{tc,O_2}}$ of 0·93 kPa after 30 min in the erect position, and a median fall of 3·74 kPa in the $P_{\mathrm{v,O_2}}$ over the same period. However, statistical analysis failed to show any significant correlation between the rise in $P_{\mathrm{tc,O_2}}$ and the fall in $P_{\mathrm{v,O_2}}$, indicating the absence even of an inverse linear relationship between the two parameters.

We have demonstrated in this study that raised venous oxygen tensions are present in patients with varicose veins. These can be explained from a knowledge of the physiological mechanisms that control the circulation. There is no need to invoke the presence of arteriovenous communications as a contributory factor in the pathogenesis of varicose veins.

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Adenocarcinoma of the cardia: treatment by thoracoabdominal R_3 radical gastrectomy

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The complications and mortality rate of R_3 radical gastrectomy using a left thoracoabdominal approach were studied in 38 patients with adenocarcinoma of the gastric cardia. There were two hospital deaths and two anastomotic leaks. There was a high rate of complications following surgery (subphrenic abscess, eight; severe chest infection, five; aspiration pneumonia, two; wound infection, two; and reactivation of tuberculosis, one). The hospital stay ranged from 11 to 39 days (median 21 days). Thirty-five patients had microscopic evidence of serosal involvement (S_2). Thirty-three of the patients had lymph node metastases and 17 patients had involvement of N_2 nodes. Four patients had histological evidence of residual suture line tumour, but only two of these returned with recurrence at the anastomosis. Follow-up (median 3 years) revealed that splenic artery nodal involvement (N_2) did not worsen the prognosis after radical resection. Despite a high complication rate, thoracoabdominal radical gastrectomy is associated with an acceptable perioperative mortality rate, adequate symptom palliation and encouraging medium-term survival. The left thoracoabdominal approach gives excellent exposure for radical resection of cancer of the gastric cardia and should be the procedure of choice for curative resection of this tumour.

Keywords: Adenocarcinoma of the cardia, R_3 radical gastrectomy, pancreatectomy

The management of patients with cancer of the cardia is controversial[1]. Many surgical approaches have been advocated[2] and the issue is further complicated by many series that have considered adenocarcinoma of the cardia together with squamous lesions of the lower oesophagus as well as adenocarcinoma arising from Barrett's oesophagus[3–5]. Adenocarcinoma of the cardia differs in aetiology, incidence, behaviour and response to treatment from carcinoma of the oesophagus and should be considered as a distinct disease entity.

Carcinoma of the cardia invades locally and spreads to the coeliac, lesser curvature, splenic, para-aortic and splenic artery (suprapancreatic) nodes We have adopted total gastrectomy and radical lymph node dissection (R_3)[6] for the treatment of patients with adenocarcinoma of the cardia. We present the results of this operation in our first 38 patients.

Patients and methods

From 1984 to 1989 50 patients with adenocarcinoma involving the cardio-oesophageal junction or the fundus of the stomach were admitted to the Department of Surgery at the Prince of Wales Hospital in Hong Kong. Patients with squamous cell carcinoma of the oesophagus, linitis plastica involving the gastric corpus, and tumours arising from Barrett's oesophagus were excluded from consideration. Forty patients (80 per cent) underwent surgical exploration and 38 patients (76 per cent) had a radical resection These 38 patients form the basis of this report.

The age of the patients ranged from 33 to 79 years (mean 62·1 years). There were 30 men and eight women. Thirty-six patients presented with dysphagia.

The patients were explored through an oblique abdominal incision along the line of the eighth rib. The wound was extended to a thoracoabdominal incision along the bed of the eighth rib if the tumour was resectable The criteria for radical resection as recommended by the Japanese Research Society for Gastric Cancer[6] were tumour confined to the gastric wall (S_{0-2}) with no peritoneal metastases (P_0), macroscopic nodal involvement up to N_{1-2} level and the absence of liver metastases (H_0). The absence of liver metastasis was determined before operation by ultrasonography and confirmed at operation by palpation.

The greater omentum was detached from the transverse colon The gastroepiploic vessels were ligated at their origin The duodenum was transected 2 5 cm beyond the pylorus and the stump was closed The porta hepatis was dissected from the hilum downwards so that the common hepatic artery and the portal vein were bared of nodes and adventitial tissue. The lesser omentum was detached from the liver and the accessory hepatic artery, if present, was ligated. The spleen and pancreas were mobilized by division of the lienorenal ligament. The diaphragm was split in a radial fashion, with excision of a cuff of diaphragm around the oesphagus The pancreas was transected at the level of the inferior mesenteric vein The pancreatic duct was transfixed with silk sutures and the cut end of the pancreas was oversewn. Total gastrectomy, with the *en bloc* removal of the distal oesophagus, greater and lesser omentum, spleen, distal pancreas, and lymph nodes in the portal, retropancreatic, para-aortic, paracardial and coeliac regions, was performed. Reconstruction was achieved by Roux-en-Y oesophagojejunostomy. Thirty-six anastomoses were stapled with the EEA® (US Surgical Corporation, Connecticut, USA) (28 mm, 28 cases, 25 mm, eight cases). Twenty-four anastomoses (including two hand-sewn anastomoses) were constructed in an end-to-end fashion while 14 were constructed end-to-side. The enteroenteric anastomosis was hand sewn with two layers of absorbable suture.

Results

Operative findings and histology

The operating time varied from 180 to 315 min with a median of 240 min. Median blood loss was 1200 ml (range 500–2900 ml). The median duration of hospital stay was 21 days (range 11–39 days).

Of the 38 tumours removed, four were well differentiated, 13 were moderately well differentiated and 21 were poorly

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Table 1 *Nodes involved in adenocarcinoma of the cardia*

	No. of patients with involved nodes
Lesser curve (N_1)	25 (66)
Paracardial (N_1)	20 (53)
Greater curve (N_1)	13 (34)
Splenic artery (N_2) (suprapancreatic)	14 (37)
Left gastric artery (N_2)	11 (29)
Splenic hilum (N_2)	8 (21)
Common hepatic artery (N_2)	2 (5)
Portal (N_3)	2 (5)

Values in parentheses are percentages

differentiated adenocarcinomas. Twenty-five tumours (66 per cent) were found to be of the intestinal type according to Lauren's classification[7]; 12 tumours were of the diffuse nature (32 per cent); and one lesion was unclassified. The median gross length of the oesophageal resection margin was 5 cm (range 4–8 cm). Four patients had histological evidence of residual suture line tumour (11 per cent). Each of these patients had the diffuse type of tumour. At operation, the regional lymph nodes were palpably enlarged in 21 patients but there was histological confirmation of nodal metastasis in 33 patients (87 per cent). Fourteen patients had involvement of the first tier of lymph nodes (N_1) (37 per cent), 17 patients had N_2 disease (45 per cent) and a further two patients had involvement of the third tier of nodes (5 per cent) (*Table 1*). Serosal involvement (S_2) was found in 35 patients (92 per cent) but local spread to the pancreas (S_3) occurred in only one case. Two patients with splenic artery (suprapancreatic) node involvement (N_2) had no evidence of N_1 disease.

Morbidity and mortality

The commonest single complication was subphrenic abscess, which occurred in eight (21 per cent) of the patients. Two of these required surgical drainage, four were drained percutaneously and two resolved spontaneously. Five patients developed severe chest infection. Two further patients developed aspiration pneumonia and required ventilatory support. Another patient had reactivation of tuberculosis which led to a prolonged hospital stay Two patients developed anastomotic leakage and were treated conservatively; in one the problem resolved on total parenteral nutrition, the other died from overwhelming sepsis on the eighth day after operation. Two patients had wound infection, one as a result of necrotic cartilage at the costochondral junction, the other because of a stitch granuloma. Both responded well to local treatment.

There were two hospital deaths (5 per cent). One patient, who presented with massive bleeding from the tumour, underwent the procedure on an emergency basis. She developed a coagulopathy despite replacement of fresh frozen plasma and platelet concentrates and died 2 h after operation. The other death occurred in one of the two patients who developed anastomotic leakage.

Follow-up

All patients were followed up, and were noted to have lost weight at 3 months compared with their premorbid state. The median period of follow-up was 36 months (range 4–60 months). The outcome is summarized in *Table 2*.

The survival rate was 52 per cent after 1 year, 28 per cent after 2 years and 23 per cent after 3 years. Of the 14 patients with positive splenic artery (suprapancreatic) nodes (N_2), four are currently well and clinically disease-free, compared with three of the 14 patients with N_1 disease.

Benign anastomotic stricture developed in five of the 36 patients (14 per cent) who left hospital. Normal swallowing was restored after one or two sessions of endoscopic dilatation with pneumatic balloons or Savary–Gillard bougies. Three other patients developed malignant recurrence at the anastomosis. Only two of these patients had histological evidence of residual suture line tumour. The malignant lesions were treated with laser therapy which provided adequate palliation of dysphagia until death from distant metastases. All other patients had normal swallowing at the time of death or to present follow-up.

Discussion

Adenocarcinoma of the cardia is a relatively uncommon neoplasm. It carries a worse prognosis than squamous carcinoma of the oesophagus[8]. Confusion has arisen over interpretation of previous series due to the lack of histological distinction from other tumours found at the cardio-oesophageal junction. In contrast to other reported series all patients in this study had adenocarcinomas originating at the cardia.

Controversy over the surgical approach to these lesions and its radicality has continued for many years[9]. Surgeons advocating extensive resection base their argument on histopathological evidence of the mode of spread of adenocarcinoma[2]. Other groups have advocated transhiatal oesophagectomy[10], two-stage oesophagogastrectomy[11] or proximal subtotal gastrectomy[12] without pancreatic or portal dissection, laying stress on lower morbidity and mortality rates and the low incidence of positive resection margins. We advocate the left thoracoabdominal approach because it allows radical gastrectomy with lymph node dissection including pancreatic and splenic artery nodal clearance for what is a gastric and not an oesophageal malignancy. Positive lymph nodes were found in 87 per cent of our patients, with nearly one-half having spread to N_2 level. Transhiatal oesophagogastrectomy with gastric pull-up would have left lymph node metastases in these patients and precluded the possibility of cure. Indeed any procedure preserving the stomach and its blood supply in our patients could have resulted in residual nodal disease. Furthermore, two patients with no evidence of lesser or greater curve nodal disease (N_1) had positive nodes in the splenic artery (suprapancreatic) chain (N_2) – so-called 'node skipping'. These patients would not have had a potentially curative procedure if a total gastrectomy without radical lymph node clearance had been carried out. The single patient with direct spread to the pancreas is still alive at 20 months with no evidence of recurrence.

In adenocarcinoma affecting the cardia the reported frequency of lymph node spread in the splenopancreatic regions is between 20 and 40 per cent[13,14]. Thirty-seven per cent of our patients had histologically proven splenopancreatic lymph node metastases. Watanabe and Sakuma[15] and Kishimoto and Koga[16] have reported better survival rates with patients having pancreatic resection for gastric cancer. Koga *et al.*[13], however, found a lower survival rate in patients who had splenectomy or pancreaticosplenectomy in addition to gastrectomy for gastric cancer. It was suggested that the splenic resection could adversely affect immunity in gastric cancer. At present this hypothesis is still conjectural. If the pancreatic resection had not been performed, over one-third of our patients would have had residual tumour left in the abdomen

Table 2 *Outcome following R_3 radical resection for adenocarcinoma of the cardia*

Review period	No. of patients eligible for assessment	No. dead	No of deaths due to carcinoma
0–6 months	36	4	4
6 months to 1 year	28	7	7
1–2 years	15	7	7
2–3 years	7	3	2
3–4 years	4	1	0
4–5 years	3	1	0

Factors that influence morbidity and mortality rates after gastrectomy for cancer include the extent of organ resection[17,18], the extent of node dissection[19] and the experience of the surgeon[20]. The surgeons participating in this series all have a special interest in upper gastrointestinal tract cancer surgery. The operative morbidity rate in our series was high with a 21 per cent incidence of subphrenic collections. More than one-quarter of patients developed severe chest complications. Although the thoracoabdominal approach has been reported to have a high incidence of respiratory complications[21], our figures are no worse than those of series using a two-stage procedure[12]. Our patients had pancreatic, splenic and portal lymph node dissections which undoubtedly contributed to the morbidity rate but did not appear to increase mortality rate. Despite this high morbidity rate and long hospital stay the operative mortality rate in our series was low (5 per cent) and compares well with other series which included patients having less radical resections[5,11,22,23].

Anastomotic leakage after oesophageal anastomosis carries an ominous prognosis. This complication occurred in only two patients in our series, resulting in one death. No difference was noted between end-to-end and end-to-side oesohagojejunal anastomoses. Because only two patients had hand-sewn reconstruction a comparison with stapled anastomoses could not be made. We suspect that the routine use of the EEA stapler may contribute to a low leakage rate.

Despite attempts to remove as much oesophagus as possible, four patients still had tumour at the resection margin, reflecting the tendency of lesions of the cardia to spread proximally. In the left thoracoabdominal approach the length of oesophagus that can be resected is limited. The alternative approach of Lewis–Tanner oesophagogastrectomy, with the anastomosis in the right chest, allows more oesophagus to be resected but leaves behind most of the stomach and its lymph nodes. The Lewis–Tanner approach also does not allow wide excision of the tissues adjacent to the tumour, i.e. at the level of the diaphragm, under direct vision. Of the four patients who had histologically proven tumour in the resection margin (staple rings), only two developed local recurrence. Both of these patients had tumours of the diffuse type (Lauren's classification). This finding confirms Husemann's observations regarding the high incidence of local recurrence in diffuse-type carcinomas[24]. The recurrence in the patient without positive suture line involvement may be explained by local disease in paraoesophageal tissues or by implantation rather than the presence of residual tumour at the anastomosis.

The quality of survival of the patients in this series was satisfactory. Ninety-four per cent of patients who left hospital were swallowing normally at the time of follow-up or at death and only one patient (with local malignant recurrence) returned with a gastrointestinal bleed. As a result of the total gastrectomy, all patients complained of fullness after meals and lost weight compared with their premorbid state. It is difficult to reach definite conclusions about the benefit in terms of length of survival in this group because the follow-up period is still short. None the less, only two patients living for 2 years after radical resection subsequently died from disseminated cancer and, of the 18 patients operated on 3 years ago or more, four are alive and well with no evidence of recurrence. As 92 and 87 per cent respectively of our patients had serosal and nodal involvement, the results can be considered encouraging and are in keeping with other experience of radical surgery for gastric cancer in the West[25]. The advanced stage of the disease at presentation also mirrors the experience in western Europe[26].

In summary thoracoabdominal total gastrectomy with radical lymph node dissection (R_3) for carcinoma of the cardia can be performed with an acceptably low mortality rate. Although distal pancreatectomy may have added to the morbidity it did not result in significant mortality. The operation provides good palliation and encouraging medium-term survival rates.

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Eradication of oesophageal varices recurring after portal non-decompressive surgery by injection sclerotherapy

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The results of injection sclerotherapy for oesophageal varices which recurred after portal non-decompressive surgery were analysed retrospectively to evaluate its efficacy. We treated 60 consecutive patients with portal hypertension; 19 were treated on an emergency basis, seven electively and 34 on a prophylactic basis. All acute bleeding was controlled with one session of sclerotherapy using a transparent overtube. After eradication by sclerotherapy, no bleeding episodes occurred and there was no recurrence of the varices, except in three uncompliant patients, during a mean follow-up period of 33·1 months. Bleeding from a gastric ulcer and gastritis occurred in one patient each. Oesophageal stenosis occurred in nine (15 per cent) patients and gastric varices developed in two (3 per cent) patients. Twelve patients died, five from liver failure and six with hepatoma, but there was no bleeding from the gastrointestinal tract. The overall 4-year survival rate was 80 per cent. We recommend the use of sclerotherapy as the primary treatment for recurrent oesophageal varices.

Keywords: Sclerotherapy, oesophageal varices, recurrence, surgery

There is controversy regarding the treatment of recurrent oesophageal varices after non-decompressive surgery in patients with portal hypertension. Variceal rebleeding was reported in 6·9 per cent of patients undergoing this form of surgery in Japan[1]. Rebleeding after all forms of portal surgery is rare but poses major problems because of the fact that these are high risk patients who experience a high morbidity[2] and mortality rate[3,4].

Injection sclerotherapy has proved effective in controlling acute variceal bleeding in approximately 95 per cent of patients[5,6]. However, the mortality rate in patients with poor liver function (Child's grade C) may be 100 per cent when oesophageal transection is performed after failure of conservative treatment, including injection sclerotherapy[7]. We have developed a new transparent overtube which has facilitated safe and secure sclerotherapy[8,9].

The present study is intended to examine the results of injection sclerotherapy in such patients who rebleed after portal non-decompressive surgery.

Patients and methods

Patients

Sixty consecutive patients underwent endoscopic injection sclerotherapy for oesophageal varices which recurred after portal non-decompressive surgery. All treatments were undertaken in Kyushu University Hospital from January 1984 to January 1987. There were 43 men and 17 women with a mean(s.d.) age of 52·0(8·5) years (*Table 1*). The aetiology of the portal hypertension was posthepatitis liver cirrhosis in 57 patients, idiopathic portal hypertension in two patients and prehepatic portal obstruction in one. Hepatocellular carcinoma was present in six patients at the time of sclerotherapy. The severity of liver disease was classified into three grades according to a modified Child's classification[10]; Child's grade A in 17, Child's grade B in 35 and Child's grade C in eight patients. The initial operations were transabdominal oesophageal transection in 24 cases, selective shunt (left gastric caval shunt and distal splenorenal shunt) in 23, cardiectomy in four, total gastrectomy in five, and Hassab's operation in four. Angiography was performed in all of the patients who had a selective shunt and in all cases the shunt was shown to be not patent. No patient had undergone sclerotherapy before surgery. Sclerotherapy was taken to be indicated in patients who were bleeding or who had a history of bleeding from oesophageal varices, or in whom the varices had developed to a moderate or large size (F_2, F_3) with one of the following signs: red wale marking (++, +++), cherry red spot (++, +++) and haematocystic spot[11]. The mean(s.d.) follow-up period from the time of primary surgery to that of the initial session of sclerotherapy was 55·6(64·0) months.

Sclerotherapy

Sclerotherapy was carried out in 19 patients in emergency circumstances to control bleeding and electively in seven patients who had bled but in whom the bleeding was controlled. In 34 patients oesophageal varices had recurred, and although these patients had not bled, they showed

Table 1 *Data on 60 patients undergoing injection sclerotherapy for recurrent oesophageal varices*

	Acute	Elective	Prophylactic
No. of patients	19	7	34
Age, years	49·1(9·8)	49·1(4·7)	54·1(7·9)
Sex, M.F	14·5	6·1	23·11
Liver disease			
Liver cirrhosis	19	7	31
Idiopathic portal hypertension	0	0	2
Extrahepatic obstruction of the portal vein	0	0	1
Liver function			
Albumin, g/l	30·2(5·1)	35·3(4·2)	35·1(4·4)
Bilirubin, μmol/l	24·0(1·0)	24·0(1·9)	22·3(1·2)
Prothrombin activity, %	62·8(19·0)	66·3(19·9)	75·0(21·0)
Indocyanine green test R15, %*	33·9(13·8)	39·9(12·7)	30·9(14·0)
Child's score[10]	8·8(1·7)	8·3(1·9)	6·8(1·4)
Child's grade			
A	1	1	15
B	13	5	17
C	5	1	2

Values are mean(s.d.), * normal range 0–10 per cent

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signs associated with a risk of future haemorrhage as defined by Beppu *et al.*[11]

The initial session of sclerotherapy was performed using a newly designed transparent overtube (K-S tube, Olympus, Tokyo, Japan)[2] which provides a clear field of vision and facilitates precise injection of sclerosant into the varices. The sclerosant used was 5 per cent ethanolamine oleate solution and 1–3 ml was used at each injection site The maximum dose of sclerosant used in one session was 30 ml. Sclerotherapy was repeated once a week until all of the oesophageal varices had been eradicated In the initial and second sessions, the sclerosant was injected into the varices; a paraoesophageal injection was added after the third session, a time when the main variceal channels and small venous channels had been thrombosed. Complete eradication was obtained after shallow ulceration had formed circumferentially around the lower oesophagus, in all patients except one[9]

Follow-up

For all of these patients, endoscopy was undertaken every 3 months after the last session of sclerotherapy. The mean(s.d.) follow-up period was 33 1(13·6) months, the range being from 1 to 59 months.

Statistical analysis

The data are expressed as mean(s.d). Statistical significance of difference was analysed by Student's *t* test. Survival rate was determined using the Kaplan–Meier method.

Results

Clinical and endoscopic characteristics

The endoscopic appearances of the oesophageal varices were comparable in terms of size and redness among the acute, elective and prophylactic cases. These patients enjoyed relatively good liver function as only eight of the 60 belonged to Child's group C; however, in those who had operations after bleeding, either emergency or elective, liver function was poorer than those treated prophylactically (*Table 1*).

Control of acute bleeding

Acute variceal bleeding in 19 patients was controlled with one session of emergency endoscopic sclerotherapy; no major complications occurred. In one patient who died from liver failure the day after sclerotherapy, there was no bleeding. Sclerotherapy eradicated the oesophageal varices in the remaining 18 survivors. In seven patients, bleeding was controlled with conservative treatment, including a Sengstaken–Blakemore tube, and sclerotherapy was then performed on an elective basis.

Variceal eradication

Oesophageal varices were eradicated in all patients except one, after a mean(s.d.) of 4·2(1·2) sessions. The mean(s.d.) volume of the sclerosant used for the initial to the fourth sessions of sclerotherapy was 23·4(5·6), 18·0(5·0), 11·8(5·4) and 6·4(5 5) ml, respectively. Oesophageal varices did not recur after sclerotherapy, except in three uncompliant patients. These three patients visited the hospital for the first time 6, 9, and 10 months, respectively, after the last session of sclerotherapy and recurrent oesophageal varices at endoscopy were then eradicated by repeated sclerotherapy. In two of the 60 patients, gastric varices appeared 11 and 19 months after the sclerotherapy; however, they were completely eradicted by sclerotherapy following percutaneous transhepatic obliteration of the left gastric vein by injection of pure ethanol, 50 per cent glucose and metallic coils.

There was no bleeding from oesophageal varices during the follow-up period after sclerotherapy. However, in two patients, bleeding was linked to gastritis and a gastric ulcer, respectively. Here the administration of an H_2-receptor blocker was effective and the bleeding was controlled.

Complications

There were no major complications. Minor complications included pyrexia (>38°C) (55 per cent), chest pain (52 per cent) and pleural effusion (60 per cent) as detected by chest radiography. Oesophageal stenosis was present in nine (15 per cent) of the 60 patients. In two patients with severe stenosis, bougienage using a Maloney tube (Neoplex, France) led to good results. The laboratory data before and after sclerotherapy showed no significant difference in liver function.

Survival time

Forty-eight patients are alive at the time of writing and 12 have died (*Table 2*), six from hepatocellular carcinoma, five from liver failure and one from a cerebrovascular accident. In no patient was there bleeding from the gastrointestinal tract. The overall 4-year survival rate was 80 per cent, it was 88 per cent in Child's A, 77 per cent in Child's B and 75 per cent in Child's C groups. The 4-year survival rate was 68 per cent for acute bleeders, 86 per cent for elective cases and 85 per cent for prophylactic cases

Discussion

Injection sclerotherapy is the most successful initial treatment for bleeding oesophageal varices. However, this may not be the case when an experienced endoscopist is not available in the institute to which patients with bleeding oesophageal varices are transferred. The surgeon called upon to treat such patients

Table 2 *Data on 12 patients who died following portal non-decompression followed by sclerotherapy for recurrent varices*

Patient no	Age, years	Sex	LC/HCC	Treatment	Child's grade	Cause of death	Duration of survival after EIS, months
1	48	M	+/+	Acute	C	Liver failure	1 day
2	53	M	+/−	Elective	B	Hepatoma	39
3	43	F	+/+	Acute	B	Hepatoma	11
4	69	M	+/−	Acute	B	Hepatoma	17
5	59	F	+/−	Acute	B	Liver failure	25
6	51	M	+/−	Prophylactic	B	Hepatoma	36
7	56	F	+/−	Acute	B	Liver failure	4
8	69	M	+/−	Prophylactic	B	Liver failure	3
9	53	M	+/+	Prophylactic	B	Hepatoma	8
10	46	M	+/−	Prophylactic	A	Liver failure	21
11	62	M	+/+	Acute	C	Hepatoma	1
12	67	M	+/+	Prophylactic	A	Cerebrovascular accident	22

LC/HCC, liver cirrhosis and/or hepatocellular carcinoma diagnosed at the time of the initial session of sclerotherapy, EIS, endoscopic injection sclerotherapy may then have to use the method most familiar to him or her such as combination of a portacaval shunt, oesophageal transection, distal splenorenal shunt, or devascularization. Postoperative recurrence and rebleeding from oesophageal varices following the use of these techniques constitute a serious problem because of anatomical difficulties resulting from the operation or because of the poorer prognosis that may follow surgical intervention. We found that acute bleeding from oesophageal varices could be controlled by sclerotherapy, even in patients with poor liver function, and also that varices could be completely eradicated and further bleeding or recurrence prevented in 59 out of 60 patients.

Our study included 34 patients undergoing prophylactic sclerotherapy, Controversy still surrounds the prophylactic treatment of oesophageal varices. There are controlled trials of prophylactic sclerotherapy and some, but not all, have reported improved survival rates following injection sclerotherapy[12–14]. The role of such sclerotherapy in long-term management remains an open question Prophylactic treatment depends on the endoscopic appearance of the oesophageal varices. Our method of predicting the risk of further bleeding was devised for Japanese patients[11] and is now under investigation in Europe as well as in the USA; other simpler methods have also been proposed[12].

The mechanisms involved in recurrence of oesophageal varices after portal non-decompressive surgery include: (1) inadequate devascularization at the time of initial surgery; (2) deterioration of liver function, and (3) development of further cephalad collateral veins such as paraoesophageal, diaphragmatic, lesser splanchnic and short gastric veins, or vessels of the gastric wall itself. It is well known that recurrent oesophageal varices develop to the same size or redness that is seen in the original non-treated varices. Once these varices rupture, bleeding is life threatening[15]. However, there are few descriptions of the treatment of oesophageal varices which have recurred after portal non-decompressive surgery Serious problems arise when patients with recurrent oesophageal varices or those who rebleed after surgery cannot tolerate major surgery[16]. For these reasons, we proposed that sclerotherapy was preferable for the control of variceal bleeding or eradication of the varices Effective management of bleeding from such recurrent varices depends on a specialized staff using adequate techniques. Needless to say the liver function of those patients must be carefully assessed[7]. The transparent overtube we use in the initial session of sclerotherapy[8,17] facilitates precise injection of sclerosant with a clear view of the operative field and compression of the bleeding site, before or after injection. Complete haemostasis can be obtained using our procedures, even in patients with poor liver function. With completion of eradication of the varices, there should be no recurrence as all the vascular channels have been thrombosed and removed with circumferential ulcer formation in the lower oesophagus[9]. Periodic endoscopy and additional sclerotherapy using only a small volume of sclerosant will prevent development of any small veins and bleeding will not occur.

The 4-year survival rate of 68 per cent in acute bleeders treated with sclerotherapy is superior to that achieved in acute bleeders in the literature[2,4,6,18], while the rates differ among the acute, elective and prophylactic cases since liver function differed significantly. Graham and Smith[15] stressed that any substantial improvement in long-term survival must improve survival time during the early period after haemorrhage. Thus, the early management using our procedure has led to improvement in the survival time experienced by patients with acute bleeding. For this reason, we consider that sclerotherapy is the treatment of choice for patients with acute bleeding varices. A controlled randomized study has heretofore not been feasible because of ethical laws defined in Japan.

There are characteristic minor complications after sclerotherapy for recurrent oesophageal varices, and oesophageal stricture or dysphagia occurs in 4–59 per cent of patients[19]. These complications were severe in two of our patients, probably because of extensive devascularization of the upper stomach and lower oesophagus at the time of the initial portal non-decompressive surgery. Stenosis occurred just after the third session of sclerotherapy, in both patients. Thus, more attention should be directed to the volume of sclerosant used and to the number of sessions of treatment of recurrent oesophageal varices after surgery. Gastric complications after sclerotherapy can be serious. Bleeding from a gastric ulcer and gastritis occurred in one patient each and gastric varices newly developed in two patients. Abrupt interruption of blood flow from the lesser splanchnic area to the oesophagus can induce congestion in the upper stomach, leading to an increase in portal hypertensive gastropathy and/or gastric varices. Paquet and Oberhammer[20] stated that haemorrhage occurred from fundic varices in 3 per cent of their patients after sclerotherapy. However, sclerotherapy alone in patients with bleeding gastric varices offers only temporary control of bleeding[21]. For all these reasons, we eradicate gastric varices by prophylactic sclerotherapy combined with percutaneous transhepatic obliteration of the left gastric vein.

We conclude from the observations on 60 patients followed for a mean of 33·1 months following sclerotherapy for recurrent oesophageal varices that this treatment is to be preferred to more invasive portal non-decompression to control variceal bleeding and eradicate recurrent oesophageal varices.

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The "Right Stuff": Five Nobel Prize–winning surgeons

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Alfred Nobel's will specified that his estate be placed in a fund, the interest of which was to be distributed on an annual basis "to those who during the preceeding year had conferred the greatest benefit on mankind." The first Nobel Prize in Physiology or Medicine was awarded in 1901, and its receipt is widely regarded as one of the highest accolades in science. This article reflects upon five surgeons who have been recognized as worthy of this honor. They are Emil Theodore Kocher, Alexis Carrel, Frederick Grant Banting, Werner Theodor Otto Forssman, and Charles Brenton Huggins. By winning this coveted prize these men have elevated the discipline of surgery to the summit of the scientific world. We review their legacy as an inspirational reminder of what we, the future of surgery, are capable. (SURGERY 1990;108:71-80.)

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> *There is a most intimate interdependence of physiology, pathology and surgery Without progress in physiology and pathology, surgery could advance but little, and surgery has paid its debt by contributing much to the knowledge of the pathologist and physiologist, never more than at the present time.*[1]*—William Stewart Halsted, 1904*

SURGICAL HISTORY IS A continuum with its chapters opened and closed by individuals—those who rise above their contemporaries to charter new paths and establish new standards for our entire institution. All students of surgery are familiar with the legacies of Paré, Hunter, Lister, and Halsted; they are the greats, the heroes of our profession. Of similar esteem are five surgeons who have made a unique contribution to surgery; each has left a legacy and deserves special mention in the pages that document our surgical heritage. These men, Emil Theodore Kocher, Alexis Carrel, Sir Frederick Grant Banting, Werner Theodore Otto Forssmann, and Charles Brenton Huggins, are five surgeons to have been awarded the Nobel Prize (Table I).[2, 3] In addition to their individual accomplishments, their crowning achievement may be their elevation of the discipline of surgery to the pinnacle of scientific perfection. They are surgeons on parity with the brightest minds in science. Their winning of this most coveted prize in medicine in a sense heralds the coming of age of surgery.

To fully appreciate the magnitude of the accomplishments of these men, we need to consider the historic context in which they occurred. The evolution of surgery from art to science progressed slowly.[4] It was not until the late eighteenth century, in large part because of the influence of the Scottish surgeon John Hunter that surgery established scientific roots.[5] In the nineteenth century, surgeons were gradually accepted into scientific circles and permitted to join the ranks of physicians within the hierarchy of the medical establishment.[6] Entering the twentieth century, surgery as we know it today was in its infancy. Yet within a few short years, surgeons were being recognized as the leading contributors to the field of medicine as exemplified by their being chosen as Nobel laureates. It is, perhaps, the relative youth of surgery as an accepted branch of medical science that makes their achievements so remarkable and them worthy of consideration as heroes in the history of surgery.

EMIL THEODORE KOCHER (1841-1917): NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE, 1909—"FOR HIS WORK ON THE PHYSIOLOGY, PATHOLOGY, AND SURGERY OF THE THYROID GLAND"

Kocher (Fig. 1), born in Switzerland, received his medical degree from the University of Berne in 1865. After graduation, he traveled extensively throughout

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Table I. Five surgeons to have been awarded the Nobel Prize in Physiology or Medicine

Name	*Year*	*Country*	*Prize won for . . .*
Emil Theodor Kocher	1909	Switzerland	work on physiology, pathology, and surgery of the thyroid gland
Alexis Carrel	1912	United States/France	work on vascular suture and transplantation of blood vessels and organs
Sir Frederick Grant Banting	1923	Canada	discovery of insulin
Werner Theodor Otto Forssman	1956	Germany	discoveries concerning heart catheterization
Charles Brenton Huggins	1966	United States	discoveries concerning hormonal treatment of prostate cancer

Europe visiting many notable clinics, the most prominent of which was that of Theodor Billroth in Vienna. After returning to Berne, he took a position at the surgical clinic of the university and within 7 years, at the age of 31 years, succeeded Lücke as Professor and Director of Surgery, a position he would hold for the next 45 years.

Kocher's interests and writings covered a vast array of topics in several fields of surgery. He published several articles in orthopedic surgery including techniques for reduction of fractures and shoulder dislocations and recognition of acute osteomyelitis. He described injuries to the vertebral column and posttraumatic epilepsy. Further articles covered topics including surgery of the male external genitalia, antiseptic treatment of wounds, preparation of antiseptic catgut, wound healing, mechanisms of injury after high-velocity missiles, and pediatric and adult inguinal hernias. He popularized the use of the right subcostal incision as an approach to the biliary tract (Kocher incision) and authored several publications focusing on gastrointestinal surgery, including gastric resection for carcinoma, cholecystitis, extraction of common bile duct stones, mobilization of the duodenum (Kocher maneuver), and transsacral excision of rectal tumors.

Kocher spent his entire professional career in Switzerland, an area of severe endemic goiter. This provided an extensive experience in surgery of the thyroid gland. Kocher combined antiseptic techniques, thorough knowledge of anatomy, and meticulous handling and dissection of tissues in his operative methods. Complications of tetany or recurrent laryngeal nerve injury were rarely encountered and he eventually achieved an astonishingly low mortality rate of under 0.5% for total thyroidectomy.[7] These enviable results were in contradistinction to those of Billroth, his only contemporary with a similarly large experience in thyroid surgery, who had complication rates orders of magnitude higher. Halsted, who was personally acquainted with both men, offered the following explanation:

> I have pondered the question for many years and conclude that the explanation probably lies in the operative methods of the two illustrious surgeons. Kocher, neat and precise, operating in a relatively bloodless manner, scrupulously removed the entire thyroid gland doing little damage outside its capsule. Billroth, operating more rapidly and, as I recall, with less regard for the tissues and less concern for hemorrhage, might easily have removed the parathyroids or at least have interfered with their blood supply, and have left fragments of the thyroid.[8]

Ironically, it was Kocher's extraordinary surgical technique of complete removal of the thyroid gland that led to his recognition of a postoperative condition he termed *cachexia strumipriva* or myxedema. Kocher relates his first experience with the entity:

> . . . only concerning one patient upon whom I had operated on Jan 8, 1874, has the referring physician incidentally reported that the girl had undergone marked change in her personality; indeed, he finally informed me that she had become quite cretinoid. . . . I was quite astonished at the appearance of my patient. To crystallize somewhat your impression I shall show photographs of the girl before and after the operation [Fig. 2]. At the time of the operation, according to the mother, both girls looked so much alike that they were frequently mistaken for one another. Where as in the ensuing nine years, the younger sister blossomed into a very pretty young woman, the one operated upon remained small, and has an ugly, almost idiotic appearance.[9]

Kocher subsequently recalled and examined several of his patients on whom he had performed total thyroidectomy and found an extremely high incidence of myxedema. These clinical observations formed the basis for much of the understanding of the function of the thyroid gland, which had heretofore been unknown. He provided a single explanation for congenital hypothyroidism (cretinism) and postoperative myxedema that laid the groundwork for thyroid-replacement therapy and medical and radioactive treatment of various forms of thyroid disease.

ALEXIS CARREL (1873-1944): NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE, 1912—"IN RECOGNITION OF HIS WORK ON VASCULAR SUTURE AND THE TRANSPLANTATION OF BLOOD VESSELS AND ORGANS"

Carrel (Fig. 3), a native of France, received his medical degree from the University of Lyon in 1900. He began his medical career as an instructor in anatomy and operative surgery at the Lyon Hospital and soon thereafter pursued his research work in experimental surgery. His research career took him from Lyon to the University of Chicago (1905 to 1906) and eventually to New York, where he became a full member of the Rockefeller Institute for Medical Research in 1912 until his retirement in 1939. He was a unique individual whose interest extended beyond the laboratory and the operating theater. He served as a major in the French Army Medical Corps during World War I, where he developed an antiseptic solution (Carrel-Dakin solution) for sterilization of wounds. During World War II, he would serve a 1-year term with the French Ministry of Health. Carrel authored best-selling books in philosophy (*Man, The Unknown*[10]) and became a firm believer in extrasensory perception and supernatural powers of the human mind. During his later years, he headed the Carrel Foundation for the Study of Human Problems.

In 1902, while still in Lyon and only 2 years out of medical school, he published a technique of blood vessel anastomosis that would form the basis for all his subsequent works.[11] In his Nobel address, this elegant technique is described:

> The termino-terminal anastomosis [Fig. 4] is effected by bringing the extremities of the blood vessels into contact, no traction being necessary. The ends are united by the retaining stitches located in three equidistant points of their circumference. By traction on the threads the circumference of the artery can be transformed into a triangle and the perimeter can be dilated at will. Then the edges of each side of the triangle are united by a continuous suture whilst they are under tension. During the suture great care is taken to approximate exactly the surfaces of section of the wall. . . . The union of the extremities is made by eversion of the edges, which are united, not by their surface of section, but by their endothelial surfaces. An inversion of the edges would be very dangerous and would provide the formation of a thrombus.[12]

Carrel used his technique in a variety of ways including autogenous vein interposition grafting, patch angioplasty, synthetic replacement of portions of the aortic wall, and interposition of vena caval grafts in the thoracic aorta. He described the method of harvesting a cuff of parent vessel along with an organ's main vessel as a means of facilitating vascular anastomoses, commonly known as a Carrel patch. He was the first to suggest the use of shunts during thoracic aortic cross-clamping as a means of preventing spinal cord ischemia. In Carrel's 1910 address to the American Surgical Association, he described mitral valvulotomy and annuloplasty, ventricular aneurysmectomy, and coronary artery bypass.[13] It would take two generations of surgeons the world over to accomplish what Carrel realized near the turn of the century.

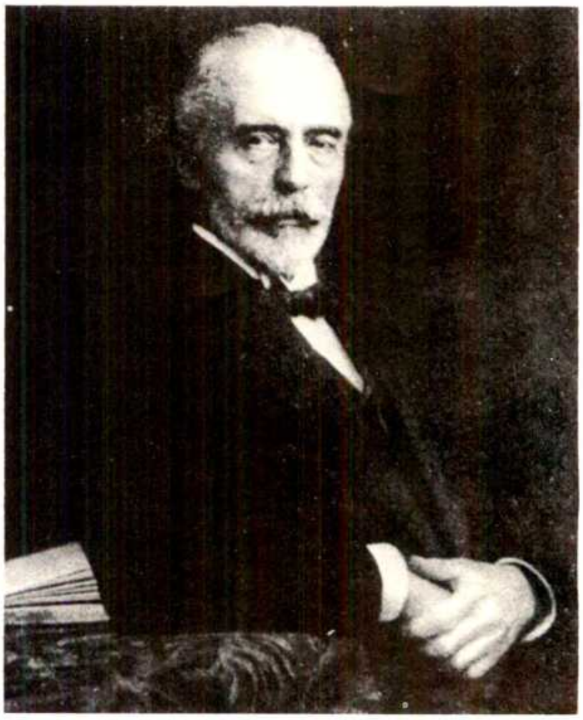

Fig. 1. Emil Theodor Kocher (1841-1917).

Carrel was a pioneer in organ transplantation. His ability to suture blood vessels allowed him to experiment with autotransplantation and xenotransplantation of numerous organs including thyroid, spleen, ovary, and kidney, as well as limb reimplantation. While at the Rockefeller Institute, Carrel worked with Charles A. Lindbergh on techniques for tissue culture and organ preservation, culminating in their coauthorship of a book entitled *The Culture of Organs*.[14] In addition, the two made national headlines with the perfusion apparatus they developed for whole-organ preservation (Fig. 5). Carrel summarized his experience with organ transplantation in a letter to Theodor Kocher dated May 9, 1914:

> . . . concerning homoplastic transplantation (from one animal to another) of organs such as the kidneys, I have never found

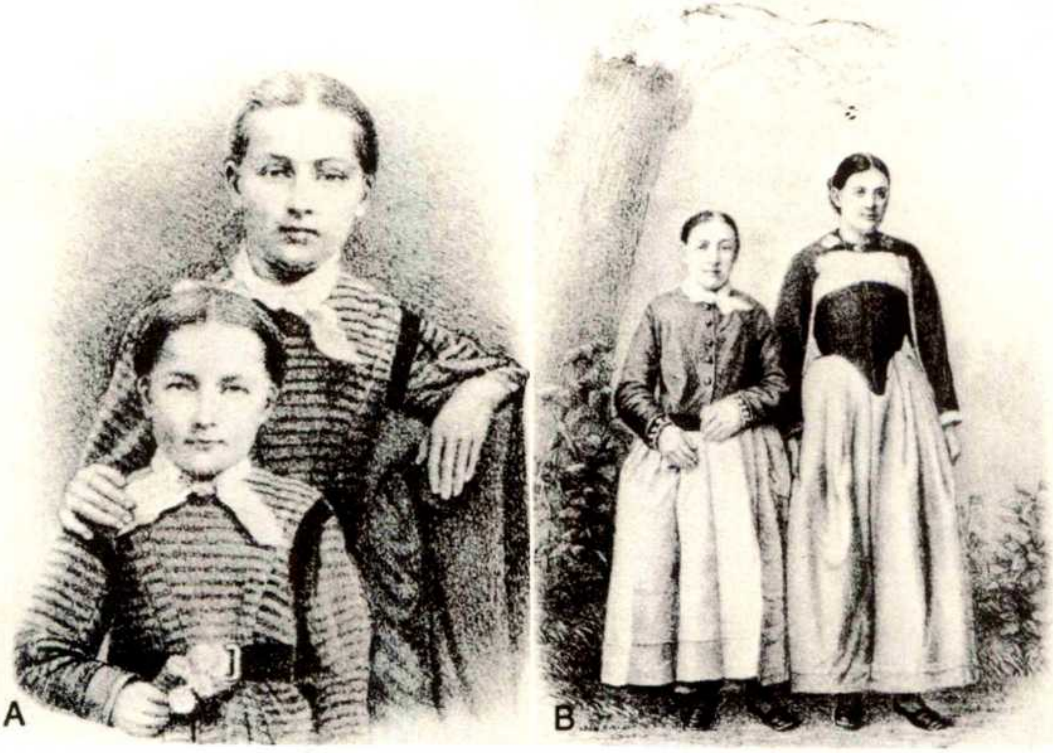

Fig. 2. The case of Maria Richsel. **A,** The older and taller patient on whom Kocher had operated in a preoperative photograph with her younger sister. Nine years after total thyroidectomy, the dwarfed and stunted patient is again photographed with her now-taller younger sister **(B).**

positive results to continue after a few months, whereas in autoplastic transplantation the result was always positive. The biological side of the question has to be investigated very much more and we must find out by what means to prevent the reaction of the organism to a new organ.[15]

The implications of Carrel's work and the insight he demonstrated regarding his observations in the fields of vascular and transplantation surgery are self-evident.

SIR FREDERICK GRANT BANTING (1891-1941): NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE, 1923—"FOR THE DISCOVERY OF INSULIN"

Banting was born in Alliston, Ontario, Canada, and received his medical degree from the University of Toronto in 1922. Before obtaining his doctorate in medicine, he served in the Canadian Army Medical Corps during World War I and earned the military cross for heroism under fire. After the war, he served as resident surgeon in orthopedics at the Hospital for Sick Children in Toronto. During the course of his medical school training, he lectured in orthopedics at the University of Western Toronto and developed an interest in diabetes research. This interest took him to the laboratory of the prominent physiologist, Professor John James Richard McCleod, at the University of Toronto in 1921. Banting's efforts during the next 2 years would lead to their shared receipt of the Nobel Prize.

The relationship between the pancreas and the secretion of insulin from the islets of Langerhans to diabetes mellitus had been appreciated for some time before Banting's work. However, previous attempts at isolation of insulin from pancreas had failed. In addition, administration of pancreatic extracts to diabetics did nothing to treat the condition. Banting hypothesized that these failures were the result of the enzymatic degradation of insulin (or, as he termed it, *isletin*) by the then-hypothetical protease trypsin. In 1921 Banting was joined in his laboratory by an eager young physiology student named Charles H. Best (Fig. 6). Together they conducted a series of experiments in which they ligated the pancreatic ducts of dogs and, after a period of 10 weeks, removed the now-atrophic gland that was relatively devoid of enzymatic proteins. They prepared a crude pancreatic extract by grinding pieces of the gland with sand followed by dissolution with a salt so-

Fig. 3. Alexis Carrel (1873-1944).

lution. The now-pancreatectomized dogs would become profoundly hyperglycemic and slip into diabetic coma unless given this extract by either a subcutaneous or intravenous route. Untreated pancreatectomized dogs were uniformly dead within 2 weeks, whereas life could be sustained for 10 weeks or more when the extract was given.[16]

They wasted no time in carrying their early encouraging laboratory results to the bedside. Within 8 months of their initial experiment, the first successful human application of insulin was accomplished. On Jan. 11, 1922, Banting described their encounter with a 14-year-old boy suffering from the end stages of diabetes mellitus as follows:

> He was pale and emaciated; he weighed only 60 pounds; his muscles were flabby; his dry hair was falling out. The odor of acetone was on his breath; his urine was loaded with sugar . . . and the proportion of sugar in his blood was very high. According to all precedents in the treatment of diabetics he should have gone into a coma and died within a few days, weeks at best. . . .
>
> A small dose of a weak solution of insulin was injected under the boy's skin. Within a few hours his blood sugar level had dropped 25 percent and the sugar in his urine had decreased. At regular intervals the dose was increased gradually until at the end of two weeks the boy became brighter and more active; he looked better and said that he felt stronger.[17]

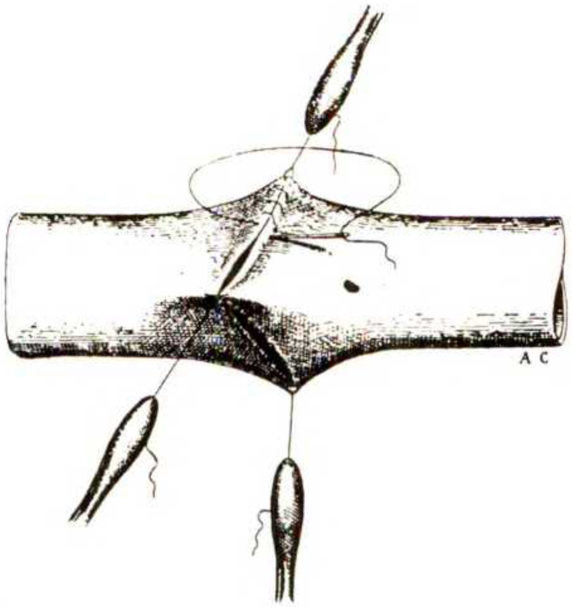

Fig. 4. Carrel's simple yet elegant depiction of his technique for terminoterminal vascular anastomosis.[11]

The potential impact of these simple yet elegant experiments was recognized immediately. In keeping with the wishes of the will of Alfred Nobel (i.e., that the prize be given annually "to those who during the preceding year had conferred the greatest benefit on mankind"), the Nobel Prize in Medicine or Physiology was awarded to Banting and McCleod in 1923. The omission of Best, and for that matter the inclusion of McCleod, as a co-recipient of the award is a controversy regarding the judgment of the Nobel Committee that rages to this day.

WERNER THEODOR OTTO FORSSMAN (1904-1979): NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE, 1956—"FOR (HIS) DISCOVERIES CONCERNING HEART CATHETERIZATION AND THE PATHOLOGIC CHANGES IN THE CIRCULATORY SYSTEM"

Forssman (Fig. 7) was born in Berlin, Germany, and completed his formal medical training at the University of Berlin in 1928. He became a clinical instructor in surgery at the August Viktoria Home at Eberswalde, north of Berlin, in 1929. After completing postgraduate study at the Charité, the City Hospital at Mainz, and finally at the Rudolph Virchow Hospital in Berlin

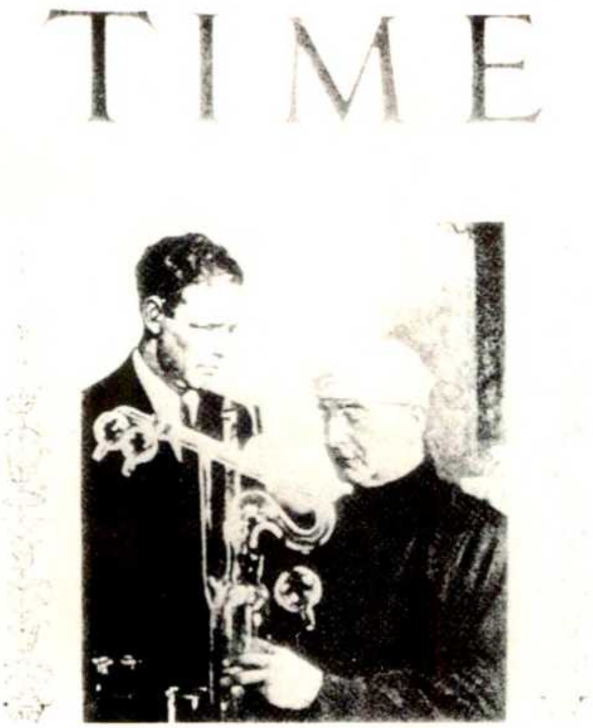

Fig. 5. Carrel and Colonel Charles A. Lindbergh share the cover of *TIME* magazine, July 1, 1935. They captured the attention and imagination of the lay press with the perfusion apparatus they designed for whole-organ preservation.

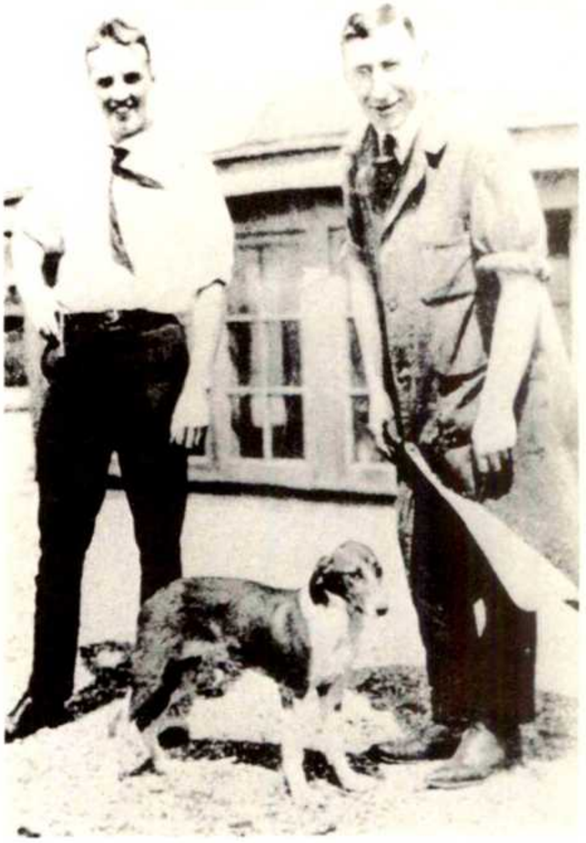

Fig. 6. Banting *(right)* and Best with a pancreatectomized dog kept alive with their pancreatic extract containing "isletin" (insulin).

where he studied urology, Forssman assumed a staff position in the Surgical Clinic at the City Hospital at Dresden in 1933. He served as a German army surgeon during World War II, achieving the rank of surgeon-major, until being taken prisoner on the western front. After his release from captivity at the end of the war in 1945, he and his wife, also a urologist, entered practice in a civilian hospital in Bad Kreuznach, Germany. In 1958 he became chief of the surgical division of the Evangelical Hospital at Düsseldorf.

While still in his surgical training at the August Viktoria Home, Forssman became frustrated with the inability to deliver drugs to the heart safely and effectively during a cardiac arrest state. The inherent danger of direct cardiac puncture encouraged him to study the possibility of transvenous heart catheterization, which had, until then, not been performed in humans. Forssman gives the following dramatic account of the first heart catheterization in 1929, which he performed on himself:

> After the success of the experiments on cadavers, I undertook the first investigation in living humans through self-experimentation. First of all, in a preliminary experiment I allowed myself to be punctured in the right elbow vein using a large bore needle. One of my surgical colleagues kindly placed himself at my disposal for this purpose. I then introduced, as in the experiments on cadavers, a well-oiled ureteral catheter through the cannula into the vein. The catheter was then easily introduced for a distance of 35 cm. of height. Because further catheterization appeared to my colleague to be too risky, we interrupted the experiment, although I felt completely well. After one week I undertook alone a further experiment.
>
> Because venipuncture with a thick needle in oneself appeared technically too difficult, I made a venesection after local anesthesia in my left elbow and introduced the catheter without resistance for its whole length, 65 cm. This distance appeared to correspond to the path from the left elbow as far as the heart. During introduction of the catheter, I had the feeling of a gentle warmth only during the sliding along the wall of the vein, similar to the feeling during an intravenous injection of calcium chloride. By intermittent movement the catheter beat against the upper and rear wall of the clavicular vein, I noticed an especially intense heat behind the collarbone

Fig. 7. Werner Theodor Otto Forssman (1904-1979).

> under the insertion of the muscles of rotation of the head; at the same time, probably through irritation of vagal branches, there was a gentle cough.
>
> The position of the catheter was proven by x-ray [Fig. 8] and indeed I observed the tip of the catheter itself in a mirror held in front of the illuminated screen by a nurse. . . .
>
> The trip from the operating room to x-ray department, which is an unusually long distance in our establishment and during which I had to ascend stairs, covering the distance on foot with the probe lying in the heart, was not associated with unpleasantness.[18]

Forssman continued his studies with cardiac catheterization and became the first to inject contrast medium successfully into the human heart, although, quite understandably, he entered this phase of his studies with slight trepidation. He wrote,

> People often ask me if I wasn't afraid. I can honestly say no, since there was no danger in inserting the ureteral catheter as long as it was done gently. But I must confess I was slightly nervous before these two contrast media experiments, and it took me a few days to make up my mind to carry out the investigation . . . But in for a penny, in for a pound; now that I'd embarked on this whole thing I felt obliged to go through with the decisive second step. Choosing and preparing the contrast medium caused me a few headaches. I tested my tolerance of the solution by filling a test tube with it and holding the mouth of the tube against the mucous membrane of my cheek for several hours. Since it did no damage I concluded the interior surface of the heart and main arteries would also tolerate it without violent reaction.
>
> . . . so it seemed to me the solution was safe. I was right. I felt no effect when I injected it, only afterwards a slight haziness, a disturbance of consciousness and vision which lasted only a second or two, presumably as the concentrated fluid first flowed through the brain.[19]

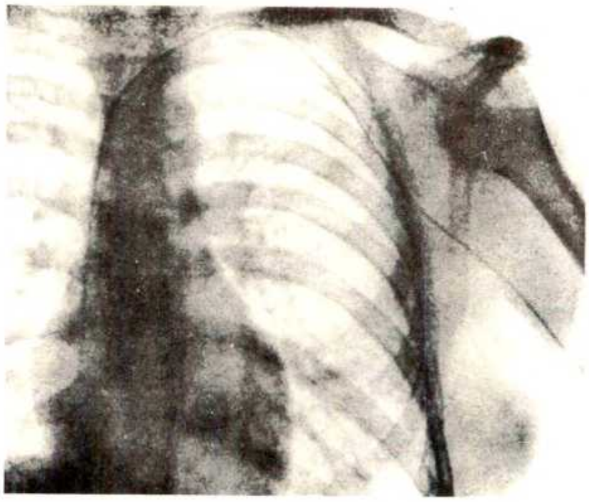

Fig. 8. Radiograph of Forssman taken in 1929 documenting the first heart catheterization. The film shows a "well-oiled ureteral catheter" in Forssman's right ventricle that was self-inserted after he performed a cutdown on a vein in his left antecubital fossa.[18]

Forssman's work ushered in the modern era of cardiology and provided the basis for our further understanding of shock states. Although he initially conceived of heart catheterization for the delivery of intracardiac medications, he immediately realized and suggested its potential usefulness as a means of studying metabolism. Unfortunately, Forssman did not receive the necessary academic or financial support required to continue his studies. On the contrary, he was subjected to intense criticism because of the perceived recklessness and potential danger of his techniques. Forssman quotes his instructor's response to his proposals as: "Young people with ideas like yours usually end up in a penitentiary!"[19]

It was not until nearly 12 years later that André Frederic Cournand and Dickinson Woodruff Richards, Jr., at Columbia University, New York, revived interest in the technique when they published their results of cardiac catheterization in humans. Forssman shared the Nobel Prize in 1956 with Cournand and Richards, 27 years after his original publication. The Nobel Com-

Fig. 9. Charles Brenton Huggins (1901-).

mittee felt justified in awarding a share of the prize to Forssman, whose work had been done so many years earlier, on the basis of a Nobel Prize Statute permitting the award to be made "for older works only if their significance has not become apparent until recently."

CHARLES BRENTON HUGGINS (1901-): NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE, 1966—"FOR HIS DISCOVERIES CONCERNING HORMONAL TREATMENT OF PROSTATE CANCER"

Huggins (Fig. 9), born in Halifax, Canada, received his medical degree from Harvard University in 1924. He went on to complete a surgical residency at the University of Michigan before becoming an original member of the faculty at the newly formed University of Chicago Medical School in 1927. An interest in the male urogenital tract ultimately led to the position of Chief of the Division of Urology, a post he maintained for 25 years until becoming Director of the Ben May Laboratory for Cancer Research.

Throughout a long and productive career, Huggins has been active in numerous areas of basic scientific research with relevance to clinical disease states. He has published extensively on the physiology of bone marrow and bone formation, the physiology and biochemistry of the male urogenital tract, prostate and breast cancer, and the biochemistry of serum enzymes and carcinogenic compounds.

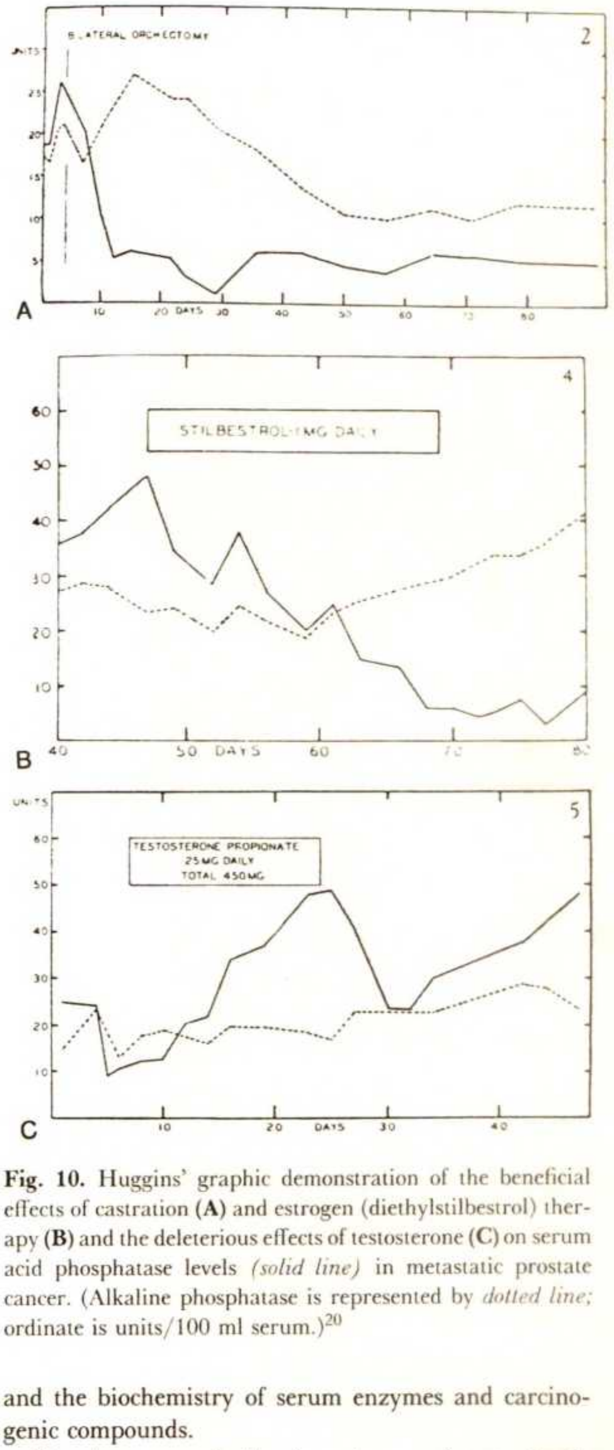

Fig. 10. Huggins' graphic demonstration of the beneficial effects of castration **(A)** and estrogen (diethylstilbestrol) therapy **(B)** and the deleterious effects of testosterone **(C)** on serum acid phosphatase levels *(solid line)* in metastatic prostate cancer. (Alkaline phosphatase is represented by *dotted line;* ordinate is units/100 ml serum.)[20]

Huggins grasped the importance of one simple observation that had been known for some time, that prepubertal castration usually prevented development of the prostate gland. In the 1930s Huggins carried out studies on normal prostate physiology and demonstrated that prostatic secretory output was amplified by testicular androgens and attenuated by estrogens and thus were competitive antagonists. These observations served as the foundation for his subsequent discoveries in human prostatic cancer.

In 1941 Huggins demonstrated a consistent elevation in serum acid phosphatase levels in 25 patients with radiographically documented metastatic prostatic cancer.[20] He found that either castration or exogenous administration of estrogen resulted in a dramatic decrease in acid phosphatase levels. Moreover, androgen injection led to an increase in baseline acid phosphatase levels (Fig. 10). In a follow-up study, Huggins reported the results of bilateral orchiectomy in 24 patients with metastatic prostate cancer and found that more than 80% of the patients had a favorable clinical response manifested by weight gain, decreased bone pain, and shrinkage of the primary lesion.[21] Four of those patients would go on to live more than 12 years. Huggins' elegant studies both elucidated a mechanism of disease and its treatment and provided the first evidence that internal host factors regulated the growth of some forms of tumors. He realized that his observations with prostate cancer may have relevance to breast cancer in women and spent several years studying the potential for hormonal manipulation of these tumors. Huggins realized that the hormones that sustain both prostate and breast cancer are formed in not only the gonads but also the adrenal glands. Using this line of reason, he became the first surgeon to perform bilateral adrenalectomy for advanced prostatic and mammary cancers.

As the pioneer in modern endocrine therapy for cancer, Huggins summarized three fundamental concepts of this new field of medicine, which remain applicable to the present day:

> (1) Some types of cancer cells differ in a cardinal way from the cells which they arose in their response to changes in their hormonal environment.
>
> (2) Certain cancers are hormone-dependent and the cells die when supporting hormones are eliminated.
>
> (3) Certain cancers succumb when large amounts of critical compounds with hormonal action are administered.[22]

CONCLUSION

These five men exemplify the best of both the art and science of surgery. An artist follows his own creative impulses; he may remain oblivious, if he so chooses, to time and tradition. The scientist is, by necessity, slave to his and others' rational hypotheses and objective experiences. The works of these five men, whether it be the meticulously detailed biochemical studies of Huggins or the brazen daring of Forssman, epitomize these two faces of surgery. Huggins summarized the essence of medical research beautifully:

> In medical research an elegant solution of a difficult puzzle is not an end sufficient unto itself. Medical research is not complete until the solution which has been achieved impinges on the lives of the people. When one discovers something which prolongs life and relieves suffering . . . it remains a meaningful legacy to the race which will last forever.[23]

There can be no doubt that each of these surgeons has provided his meaningful legacy.

Yet we should not forget that the purpose of reviewing the accomplishments of our predecessors is not to make us surgical historians but to make us better surgeons. By highlighting the achievements of these five men, we pay them tribute for what they have done for science, humanity, and our profession. But more important, we should follow the lead of these Surgeon-Nobel Laureates. Their pioneering vision is an inspiring example of the greatness of which surgery and surgeons are capable. They have earned their rightful place in the chapters of surgical history and will be forever remembered, individually and collectively, as surgeons with the "Right Stuff."

> Those therefore who estimate surgery by operation alone, & believe that nothing but long habit & practice is necessary to form the great surgeon, are grossly ignorant of the art. . . .
>
> . . . if the science of surgery, then, requires genius, knowledge, & indefatigable application to render its Professors truly respectable, what must wee think of the insolence and malevolence of those who represent it as a low mechanical art, which may be taught a butcher's boy in a fortnight.[24]—John Johns, 1769

We express our gratitude to Thomas A. Stellato, MD, Robert J. White, MD, PhD, and John A. Galat, MD, from the Department of Surgery, Case Western Reserve University, for their encouragement and helpful suggestions in the preparation of this manuscript.

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Correspondence

A Chair of Tropical Surgery

Sir

'Tropical surgery' is in a parlous state and there is a need for the surgical community of the Developed World to recognize its problems and help where it can. Mr Holcombe (*Br J Surg* 1990; **77**. 3–4) and I agree, at least, on that.

Unfortunately, Mr Holcombe does not conceptualize the problem properly. Tropical surgery is not 'a distinct subspecialty of surgery', nor is it confined to his list of exotic conditions that are peculiar to the hot and humid latitudes. The surgery that 'tropical surgeons' undertake is the surgery of the Third World, of poor people in poor countries, surgery that is poorly resourced[1] It is surgery carried out often by inappropriately trained doctors, usually working in isolation. It is frequently of poor quality. The exotic conditions he quotes are far less numerous than the universal pathology of the obstructed hernia, staphylococcal infection, peptic ulceration and genital infection but all of these are swamped by trauma· the trauma of road accidents, accidents in the home and the trauma of armed conflict that is, sadly, so frequent. 'Tropical' is the wrong adjective and conveys the wrong message Loefler[1] has suggested it be called 'Third World surgery'.

Even if I did not feel so strongly about the name I would still state, categorically, that to form a training and research centre in the developed world is a step in the wrong direction.

Though he acknowledges that, amongst the surgical problems of the Third World, it is the provision of surgical services, I cannot see how this new department of his which shall provide 'appropriate training of overseas doctors' will produce much benefit. Indeed, it is likely to do much harm They will not, for example, learn in his institute how to take skin grafts with razors and gain familiarity with the problems of the small district hospital.

His offer of 'appropriate training', even if more successful than I imagine, may have exactly the opposite effect to that which he intended. offering a course in tropical surgery in the UK, or any part of the Developed World, will threaten those struggling training programmes already in existence in the Third World The better trainees will be selected and seduced by the glamour of travel and higher salaries; the less good will stay behind. On their return, the better, now probably armed with further diplomas, will seek to enshrine the validity of their overseas training and the home-trained will remain, quite definitely, second class The Overseas Doctors' Training Scheme which he admires, though yet in its infancy, is going to have exactly the same effect and the more established it becomes the more it will prevent appropriate surgical training schemes emerging in the Third World

Though he identifies the problem of surgeons working in professional and social isolation, poor delivery of surgical services and poverty, his solution is not the right one Third World surgeons must be trained in the Third World and it is that environment that provides the most urgent stimulus for appropriate research to be undertaken. No European based department, for instance, would ever develop a portable charcoal or oil burning still for the production of sterile, particle-free intravenous fluids, such as Dr Ecookit developed in Ngora Hospital, Northern Uganda 18 months ago (Ecookit, personal communication)

The need, I suggest, is that the Third World countries, individually at first, address this unmet need for surgery rather than emphasizing increased specializations. Its medical schools must collaborate with governments in producing graduates capable of becoming district medical officers who are able to do the ten most common surgical procedures or supervise them being done by paramedics and this training must be done in the Third World. It is a training, not only of surgery but a training in management, initiative, in looking for innovation and, of course, training in dealing with limited resources. There will be a need for surgeons from the Developed World to support these locally based initiatives and help in the establishment of rural surgical institutes which could research, not only the aetiology and treatment of surgical conditions, but also the effective, feasible, cheap, low-tech manner in which to treat, for example, long bone fractures when no plaster of Paris is available. The surgical problems of the Third World are different from those of the Developed World and the important differences that exist between these two cultures are not the peculiar diseases that exist there It is a harsh lesson to learn but the Third World needs to produce its own solution aided, of course, where possible by the Developed World and their colleges and associations of surgeons.

The Association of Surgeons of East Africa has, since 1976[2], been addressing itself to the problems of surgical training and it is now actively working towards the development of rural surgical institutes staffed by a consultant cadre whose role is to train young graduate medical officers in appropriate techniques and to engage in research appropriate to local problems

Help them build their rural surgical institutes and I will support you. Attempt to build a tropical surgical institute in the Developed World and you will run the risk of being a post-colonial relic

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Tissue plasminogen activator in peripheral arterial thrombolysis

Sir

We read with interest the recent article by Berridge *et al* (*Br J Surg* 1990: **77**: 179–82) concerning the use of tissue plasminogen activator in peripheral arterial thrombosis. Our unit has recently begun to use r-TPA as the agent of choice in acute occlusions of both native vessels and grafts and we have been impressed by its superiority over previously used agents. We acknowledge the Nottingham group for their work in establishing the optimum dosage schedule[1] and for now showing that the addition of low dose heparin is not required. We would like, however, to make some additional points.

They chose to limit treatment to occlusions which had been present for 30 days or less We have had successes after treatment of occlusions present for up to 12 weeks We would suggest that the upper limits for occlusion times eligible for this treatment have yet to be established.

We feel that the inclusion of 'recent major surgery' as an absolute contraindication to thrombolytic treatment needs to be defined. Our experience with r-TPA for clearing synthetic graft thromboses has led us to use it in two patients who have had recent peripheral vascular operations We would not consider recent femoropopliteal bypass, even in the first postoperative week, an absolute contraindication although caution is obviously required

In common with other groups we have found groin haematomas to be a problem and have altered our angiographic technique to deal with this. We now leave the catheter introducer sheath *in situ* during treatment as we feel that it more effectively prevents leakage from the arterial puncture site than does the thinner angiography catheter After removal of the angiography catheter the infusion is maintained for a period of 6 h via the sheath, overcoming the problem of pericatheter thrombus in our patients. Since adopting this policy we have markedly reduced the incidence of groin haematoma.

After successful thrombolysis/angioplasty at Nottingham patients are anticoagulated, but it is not clear for how long this continues. Long-term anticoagulation in an elderly population carries significant risks of morbidity or mortality and the absence of definite proof of benefit has precluded its use in other areas of peripheral vascular work, e.g. claudication or postreconstruction. We are unaware of documented evidence of benefit following thrombolysis and have not employed it in our patients We prefer to use low dose aspirin. Our results in limb salvage are similar to those quoted in their publication. We wonder on what basis anticoagulation is used and suggest that it should not be routine until there is definite evidence of benefit.

We agree with the authors that tissue plasminogen activator is an excellent treatment option for peripheral arterial thromboses and confirm its efficacy at the low dose regime which they advocate.

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1. Earnshaw JJ, Westby JC, Gregson RHS, Makin GS, Hopkinson BR Tissue plasminogen activator. a dose ranging study in acute peripheral arterial ischaemia *Br J Surg* 1988, **74** 1196–200

Authors' reply

Sir

We would like to reply to the letter from Dawson *et al*. The limit of 30 days was selected to allow a relatively close range of duration of occlusions, this then provides efficient lysis in comparable patients. We fully agree that lesions of longer duration can be treated, albeit with a longer duration of lysis, and hence a tendency to a higher haemorrhagic complication risk. As experience with new agents such as r-TPA increases, more mature lesions will undoubtedly be accepted for lysis

Peripheral arterial graft thromboses can be lysed even in the early postoperative period, the fresh intraluminal thrombus being more susceptible to lysis than the 'mature' (cross-linked) anastomotic and wound thrombus/fibrin. However, the longer the infusion continues, the higher the risk of this also being lysed and hence causing haemorrhage. In the periphery, this risk can be monitored, and if necessary controlled by pressure whilst other specific measures are introduced. However, following intra-abdominal, intrathoracic, or intracerebral surgery this presents an unacceptable risk.

Postlysis anticoagulation rather than low-dose platelets was chosen following the occurrence of early rethromboses on patients only given aspirin in earlier work. These patients were successfully relysed and their patency has been maintained on warfarin. All patients are anticoagulated for 3 months and then transferred to low-dose aspirin.

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Bleomycin and talc for control of pleural effusions

Sir

The article on the use of bleomycin and talc for control of pleural effusions by Hamed and associates (*Br J Surg* 1989; **76**: 1266–7) was of interest. I am in complete agreement with the authors that talc pleurodesis is superior to bleomycin in control of pleural effusions; indeed, in my own experience, talc is superior to any other agent used for this purpose. Also, I agree with Dr Hamed that there is only a minimal degree of pain, and that it responds to simple analgesia without need for opiates. Why, then, do the patients who receive talc have to be fit for general anaesthesia?

We are using talc pleurodesis not only for control of pleural effusion, but also in patients with recurrent pneumothorax, chylothorax, and in selected cases of empyema[1–4]. We administer 2 g of talc in one of two ways: either insufflating it through the lumen of the mediastinoscope at the time of pleuroscopy, or injecting it as a suspension in 50 ml of normal saline through a chest tube, after evacuation of all fluid. The tube is then attached to underwater seal with suction for 3 days. With experience of over 250 cases, our results are excellent. If the talc is insufflated at the time of pleuroscopy, then general anaesthesia is necessary, but only because we do our pleuroscopies under general anaesthesia. However, in about half of the patients, we use the pleural drain route General anaesthesia is unnecessary, and was never administered to these patients.

It is unclear why Dr Hamed and associates need general anaesthesia for talc insufflation.

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Author's reply

Sir

We were glad to see that Dr Weissberg's results with talc pleurodesis for patients with recurrent pneumothorax, chylothorax and empyema mirrored the success of our recent trial and previous ones which had compared talc with mustine and tetracycline. General anaesthesia was employed in this trial and others because thoracoscopy formed an intrinsic part of the evaluation of these patients. However, if pleurodesis is being performed for a malignant effusion without a thoracoscopy being carried out, Dr Weissberg's results would certainly suggest that general anaesthesia is unnecessary.

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Wide local excision in carcinoma of the breast

Sir

We would like to comment on several of the points raised by Nicholson and Farndon (*Br J Surg* 1990; **77**: 476 (correspondence)) in reference to our paper 'Wide local excision as the sole primary treatment in elderly patients with carcinoma of the breast' (*Br J Surg* 1989; **76**· 898–90).· We accept their comments regarding the limited patient numbers which are, in fact, similar to many previous reports of conservative surgery without radiotherapy.

Clearly the study was not a randomized study comparing the effects of two methods of treatment on long-term survival, but a retrospective analysis of the results of wide local excision without radiotherapy or systemic treatment, with particular reference to locoregional recurrence and its subsequent management. Consequently, patients were not recruited uniformly throughout the period of the study. Fewer patients were treated by wide local excision in the earlier part of the study, the increased acceptability of this form of treatment led to increased numbers being included during the later years. However, the inclusion criteria, as stated in the paper, remained constant throughout.

Locoregional recurrences were defined as those in which further disease appeared in the breast, or lymph nodes became progressively enlarged or fixed. Fourteen per cent had clinically palpable, mobile nodes at presentation. Of these, only half progressed, underlying the well recognized inaccuracy of clinical staging of the axilla. Most surgeons in the UK would not employ chemotherapy in these postmenopausal patients, as suggesed by your correspondent.

Figure 1 in our paper is not misleading, it simply shows the number of patients who died with or without recurrence, the point being that in these elderly patients, deaths from other causes at least equal those directly owing to recurrence.

We agree that tamoxifen may be beneficial as adjuvant therapy, particularly in elderly patients, and it is now our policy to use tamoxifen as adjuvant therapy in selected patients. It will be apparent that this beneficial effect was not clearly established at the time of our study

Nicholson and Farndon advocate radiotherapy in all patients after conservative breast surgery even though this has not been shown to reduce mortality. This results in two-thirds of patients receiving unnecessary treatment which, as we stated, has not inconsiderable morbidity. Until local recurrence is clearly demonstrated to result in a reduced survival, the decision to use adjuvant radiotherapy remains empirical In younger patients, the psychological effects of an early local recurrence may justify the use of adjuvant radiotherapy in all cases. The situation may not be the same in elderly patients where a more conservative approach may be justified. We stand by our conclusion that it may be reasonable to undertake conservative surgery of breast carcinoma in elderly patients without routine radiotherapy, which is then available to treat those who develop recurrence.

The role of radiotherapy in conservative surgery for breast cancer is currently the subject of a prospective randomized clinical trial in the West Midlands.

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Book reviews

Intraoperative Radiation Therapy

R. R Dobelbewer, M. Abe. 260 × 185 mm. Pp. 405. Illustrated. USA· CRC Press. £127.50 hardback.

It is a feature of the 20th century that important innovative technology often arising in Europe usually reaches its highest development or application in Japan and, in close competition with North America, leaving the Europeans scrambling to pick up the trail Intraoperative radiotherapy is no exception to this. It was the German Beck who first used intraoperative radiotherapy to treat a patient with advanced pyloric cancer in 1907. In the modern sense, intraoperative radiotherapy was developed by Mitsuyuki Abe, Chairman of the Radiology Department in Kyoto in the early 1960s. There are now at least 38 institutions in Japan that have treated more than half of the 3000 patients world-wide who have received intraoperative radiotherapy for more than two dozen different types of cancer. Its introduction to the USA commenced in the 1970s, more than 10 years later. Ralph R Dobelbewer, who is the Chairman of the Radiation Therapy Department at the Medical College of Ohio at Toledo, is a leading exponent of this form of treatment and has been involved in its critical evaluation for more than a decade.

The vigorous interest shown in intraoperative radiotherapy lies with the advent of electron beam therapy allowing precise delivery of high doses of radiation with a greatly improved therapeutic ratio. Potentially, its use is of great value to the treatment of cancers normally responsive to external beam radiotherapy such as breast cancer, for certain complications can be minimized and the length of subsequent treatment with external beam radiotherapy reduced

This is an excellent, well produced book and the list of contributors is almost, but not quite, comprehensive. The 33 chapters provide a detailed description of the theory, practical application and results of intraoperative radiotherapy. It has been established that intraoperative radiotherapy is safe and that it will provide effective local tumour control in certain situations. It is equally apparent that intraoperative radiotherapy on its own will not provide magical cures for the majority of cancers but may well find an important role in conjunction with resectional surgery, electron beam radiotherapy and chemotherapy.

It is of interest that no true-blue prospective randomized trials involving intraoperative radiotherapy have been completed but comparative analyses have shown its promise in a number of areas. Thus, in a study of 211 patients with gastric cancer, who were allocated either surgery or surgery plus 20–40 Gy by intraoperative radiotherapy depending on the day of admission to Kyota University Hospitals, striking improvements in survival at 5 years were shown for patients with stages II–IV

Ongoing intraoperative radiotherapy programmes have also been established in Austria, Spain, Italy and Holland and are likely to be established in many more countries in the next decade This book is, therefore, extremely timely It is highly recommended to oncological surgeons, radiotherapists and medical oncologists wishing to familiarize themselves with the techniques involved and obtain an up to the minute review of the known clinical benefits. Health managers and hospital architects privileged enough to be involved in the development of intraoperative radiotherapy will also find it of great value

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Aids and Surgery

A. J. W. Simm, D. J Jeffries, eds 240 × 160 mm. Pp. 144. Illustrated. 1990. Australia. Blackwell Scientific Publications. £24 95 hardback

The editors state that this book is intended for 'surgeons who take an interest in aspects of medicine which impinge on and affect their own disciplines'. The need is evident for an introduction to the subject of HIV infection, and how this might affect the practice of surgery, for those surgeons who have so far encountered only a few or no such cases. The book is a compilation of contributions to a conference of the same name, held in December 1987.

This book is a curious mixture of carefully written reviews, descriptions of clinical experiences, and brief statements of unsubstantiated opinion. There are excellent chapters on the biology of the human immunodeficiency viruses, the treatment of AIDS and mechanism of action of drugs, the assessment of risks associated with blood transfusion, sterilization procedures and legal aspects of AIDS. There are thoughtful contributions with useful practical solutions for the prevention of transmission of the virus in urological surgery and fibreoptic endoscopy. However, there is considerable repetition, deliberately retained by the editors, particularly in the chapters which relate AIDS to surgical practice in general

It is unfortunate that most chapters have not been updated since 1987. In this rapidly expanding and changing field, one would expect more than two or three references to publications after 1987

This book addresses an unmet need amongst anaesthetists and surgeons of all types who are now concerned about the spread of HIV infection outside of previously defined high risk populations It may be a useful source of information on methods of prevention of transmission in some areas of surgical practice, when this information is not already available

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With Sharp Compassion: Norman Dott, Freeman Surgeon of Edinburgh

C. Rush, J. F Shaw. Pp. 314 Illustrated. 1990 Aberdeen Aberdeen University Press. £17 50 hardback

Here is a purple prosed hagiography, a mine of mixed metaphors, a dense deposit of sentiment-encrusted divots, hacked from the historical soil of early and mid-20th century Edinburgh The club used by the authors has been highly selective so that we learn little about the growth of surgery in that city: the whole scene is portrayed as a backdrop to the single minded, triumphant progress of its subject – Norman Dott. He was undoubtedly a singular man and, like so many of those neurosurgical pioneers who emerged from the Cushing school at the Peter Brent Brigham Hospital in Boston, was imbued both with a sense of the immense importance of the science and practice of surgical neurology and with the Protestant work ethic required to bring about its organization and development. Though he had these characteristics as a consequence of his heredity and the cultural influence of his native lowland Scotland, he modelled his behaviour on the puritanical zeal of Cushing with results that Edinburgh and all the world can now see – an integrated department of neurological sciences which in embryo was always his goal and largely achieved as a consequence of some devoted disciples during his lifetime

The book is obviously written, consciously or otherwise, largely for lay readers and as such it deserves every success Regrettably in my view there is little in it for the surgeon or, if they are without first hand experience of the Edinburgh scene, for those interested in events of the 1930s through the 1950s in that city Individuals such as John Fraser, James Graham, Maxwell Brown (Dott's quirky and engineeringly talented anaesthetist) and a host of others flit in and out of the pages merely as foils to the descriptions and adultations of the book's subject. There is nothing much wrong with this provided the work is not looked upon as a historical record because in this way it could misrepresent what actually happened – that dull raw material of history To take but one example it almost appears that Dott founded the famous (or infamous for the registrars who had to prepare for them) Saturday morning meetings on what it is now fashionable to call 'audit' Those of us who were there know that this is not so

The book should be read as an account of what can be done by an immensely talented man who kept his shoulder to the neurosurgical wheel with unswerving devotion as well as inspiring a similar devotion in a host of others I will leave the reader to judge whether this model is admirable or merely self centred and praise the Aberdeen University Press for the quality of their production.

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Principles of Surgical Research

R T Mathie, K. M. Taylor, J. S Calnan 240 × 165 mm. Pp 205 Illustrated 1989. London Wright. £25.00 hardback.

Research activity has an important educational role in surgical training but, in order to be effective, it demands a wide range of skills. Successful projects depend upon careful organization, adequate funding, valid methodology, accurate data collection and objective analysis. Communication skills are also important, not only for the presentation and publication of the results but also for the production of a higher degree by thesis This book deals very effectively with each of these aspects It is based on a successful course held annually at the Royal Postgraduate Medical School entitled 'Research Methods in Surgery'.

Before embarking on a research project a young surgeon would do well to take heed of the advice provided by all the contributors, each of whom has extensive personal research experience and has been involved in the supervision of research projects

The chapters are well written and full of sensible advice and suggestions. Emphasis is placed on the importance of a clear protocol and fastidious attention to detail. Although a good experimental model is the backbone of surgical research the place of 'fishing trips', 'stamp collecting' and 'wallpaper matching' as techniques in research endeavor are mentioned There are excellent and easily digestible chapters on statistical analysis, the use of computers, the importance of controlled trials and particularly on how to write and present a paper This book is valuable not only for surgeons-in-training but also for established consultants. There is a particularly interesting chapter related to research in district general hospitals and illustrates very well how audit and continuing professional education intermingles in a very positive fashion with continuing research activity.

I have no hesitation whatsoever in recommending this book to all individuals who wish to undertake a period of surgical research activity.

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Vascular Surgery

G Heberer, R J. A M. van Dongen. 197 × 273 mm Pp. 811 Illustrated. 1989. Berlin Springer-Verlag. £232.00 hardback

Vascular surgeons have preceded the bringing down of European barriers in 1992 by 20 years through active vascular societies, and this book from Heberer and van Dongen gives an excellent practical review of vascular surgery as practised in Western Europe.

The book is written by vascular surgeons from Germany, The Netherlands, Austria and Switzerland, and the German edition of this book is the 11th volume of a series of *Manuals of Surgery*. Even glancing through this text book the high standard of publication is apparent, and in particular the outstanding diagrammatic illustrations that appear on almost every page. Interestingly enough, apart from diagrams of how to do certain manoeuvres and operations, there are also diagrams on how not to do them, which are really quite valuable. Each chapter is clearly written by a surgeon with wide practical experience of his chosen subject, and much valuable advice is available to anyone contemplating any of the operations thus described. I would, for instance, recommend that everybody involved in surgery of abdominal aortic aneurysms reads the chapter by Schildberg and Valesky on the technique and management of this common problem.

Perhaps the only minor criticisms would be the occasional aberration in translation, which on the whole is of a very high standard, and the slight non-uniformity of the presentation of the references. The references derive frequently from European based journals, and in some ways this is quite refreshing, although occasional major publications from the English literature could have been usefully included

The editors state in their final sentence that, 'we hope that this manual, the product of more than 30 years of personal experience, will become a useful source of sound advice in the field of vascular surgery'. I think they have achieved this by producing a book that all vascular surgeons would benefit from reading, and those non-specialists, who occasionally find themselves confronted by a vascular problem with no assistance, could glean some useful tips from this beautifully illustrated and informative volume.

C. A. C. Clyne

Torbay Hospital
Torquay TQ2 7AA
UK

Erratum

'Splenectomy for hypersplenism in chronic lymphocytic leukaemia and malignant non-Hodgkin's lymphoma' by J. R. Delpero *et al*., *Br J Surg* 1990; **77**. 443–449.

The labels in the y-axes of **Figures 4** and **5** were inadvertently transposed. We apologise for this error and for any confusion caused to the reader.

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19–23 August 1990
Recent Advances in Oral Maxillofacial Surgery
Glasgow, UK
Information. Louise Deakin, Courses dept., The British Council, 65 Davies Street, London W1Y 2AA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong ,
Information: The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

28 August–7 September 1990
Recent Advances in Respiratory Medicine
Edinburgh, UK
Information. Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

1–6 September 1990
6th World Congress in Ultrasound
Copenhagen, Denmark
Information: Torben Larsen, Dept of Gynecology, Herlev Hospital, DK-2730 Herlev, Denmark

6–8 September 1990
2nd Congress of the European Association of Video-Surgery
Turin, Italy
6*Information*: Professor A. Gaetini, Torino Esposizioni Corso Massimo D'Azeglio 15-10126 Torino, Italy

12–14 September 1990
Carotid Duplex Technology, Hands-On Instruction
Northeast USA
Information: Patricia Aguilar, Keith Mauney & Associates Inc., 600 E. Las Colinas Blvd, Suite 250, Irving, Texas 75039, USA

15–16 September 1990
Advanced Carotid Duplex Interpretation
Northeast USA
Information: Patricia Aguilar, Keith Mauney & Associates Inc, 600 E. Las Colinas Blvd, Suite 250, Irving, Texas 75039, USA

14–17 September 1990
Annual Meeting of RCPSC
Toronto, Canada
Information: Anna Lee Chabot, Head – Meetings and Assemblies Section, Office of Fellowship Affairs, The Royal College of Physicians and Surgeons of Canada, Toronto, Canada

20 September 1990
Royal College of Surgeons of England Annual Meeting of Fellows and Members
London, UK
Information. Alison Cole, Royal College of Surgeons of England, 35–43 Lincolns Inn Fields, London WC2A 3PN, UK

20–21 September 1990
IV Annual Meeting of the European Society for Vascular Surgery
Rome, Italy
Information. Paolo Fiorani, Department of Vascular Surgery, University of Rome, School of Medicine, Policlinico Umberto 1, 00161 Rome, Italy

20–22 September 1990
Association of Surgeons in Training, 14th Annual Conference and AGM
Birmingham, UK
Information. Mr John Taylor, c/o Postgraduate Medical Centre, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TQ, UK

23–28 September 1990
Comprehensive Review and Update of What's New In Vascular Surgery
Santa Monica, California, USA
Information: Dr W. S. Moore, Professor of Surgery, Section of Vascular Surgery, UCLA School of Medicine, PO Box 24901, Los Angeles, California 90024-0901, USA

25–28 September 1990
1st International Conference on Ultrasound Angiography
London, UK
Information Mr K. N. Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

26–28 September 1990
Annual Scientific Meeting
University of Manchester
Information: Ann Muir, Association of Anaesthetists, 9 Bedford Square, London WC1B 3RA, UK

1–4 October 1990
Eurochirurgie: 92e Congres Francais de Chirurgie
Paris, France
Information Secretariat Administratif, CONVERGENCES-AFC 90, 120 avenue Gambetta, 75020 Paris, France

3–6 October 1990
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455, USA

7–12 October 1990
Future Conventions of the American College of Surgeons
San Francisco, USA
Information: Fred C. Spillman, Convention Manager, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

23–31 October 1990
Clinical Anaesthesia in the 1990s
Bristol, UK
Information. Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

28 October–1 November 1990
43nd Postgraduate Assembly
Honolulu, Hawaii
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

2 November 1990
Management of Complications Following Vascular Surgery
Newcastle-upon-Tyne, UK
Information. Mr J Chamberlain, Ward 7 Office, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

3–7 November 1990
State of the Art in Digestive Surgery
Delhi, India
Information: Convention Centre, Hotel Taj Palace Intercontinental, Sardar Patel Marj, New Delhi 110021, India

5–9 November 1990
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

13–16 November 1990
2nd International Interdisciplinary Symposium
Vienna, Austria
Information: Peritoneum and Peritoneal Access (PAX), F. Schulz, c/o Vienna Academy of Postgraduate Medical Education and Research, Alser Strasse 4, A-1090 Vienna, Austria

6–8 December 1990
1st International Symposium on Benign Breast Disease and Chemoprevention of Breast Cancer
Genoa, Italy
Information· Oncologia Clinica, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10, 16132 Genova, Italy

11–13 December 1990
5th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Joseph W C Leung, Senior Lecturer in Medicine, Prince of Wales Hospital, Shatin, Hong Kong

19–20 January 1991
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 January–1 February 1991
Second European Winter Oncology Conference
Meribel, France
Information IMEDEX B,V, PO Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information· ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

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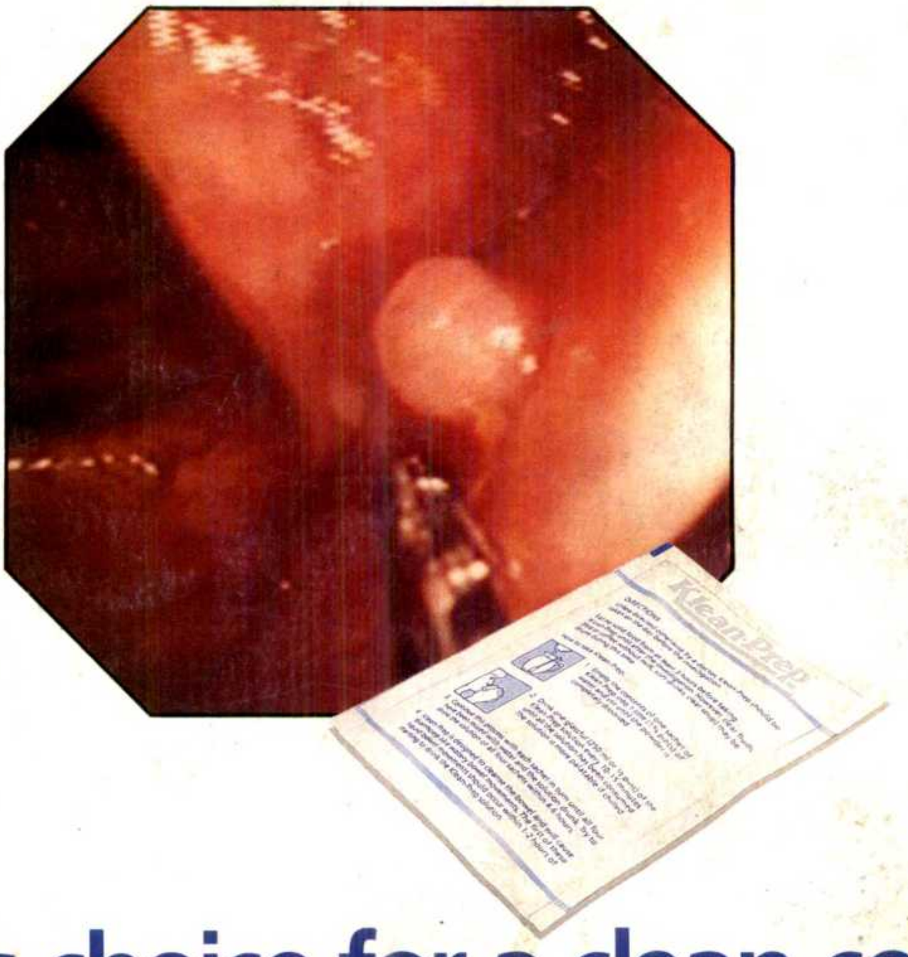

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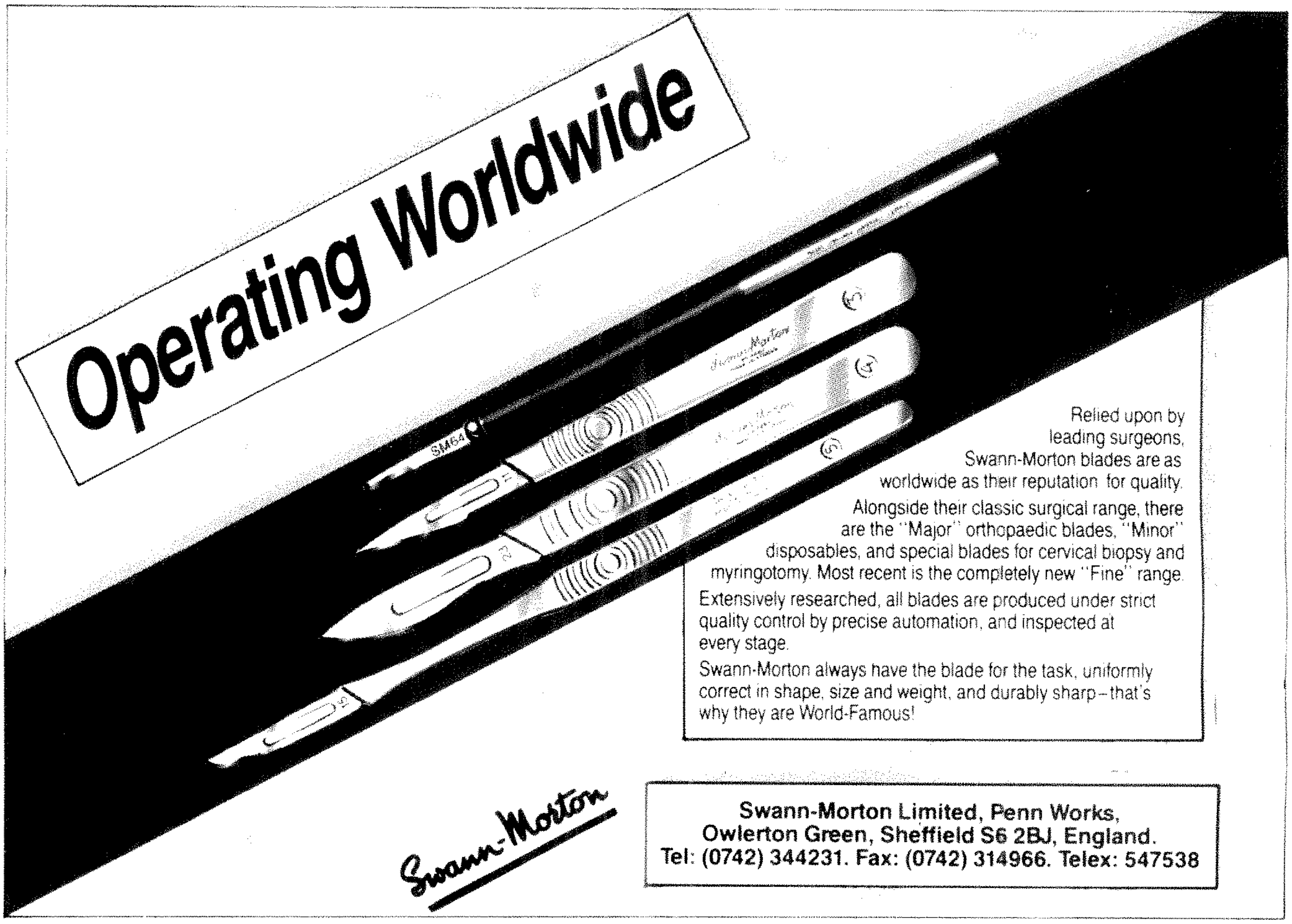

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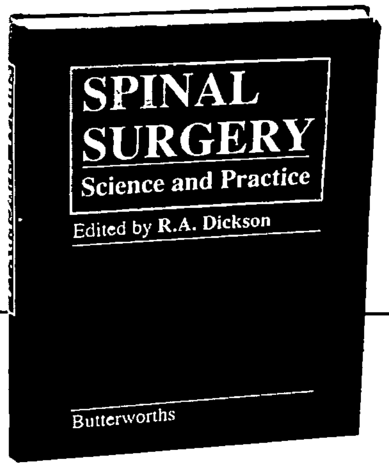

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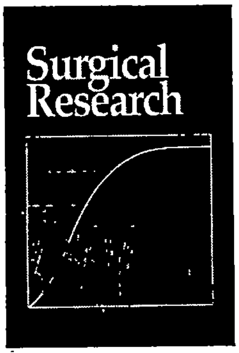

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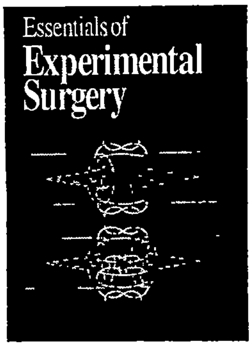

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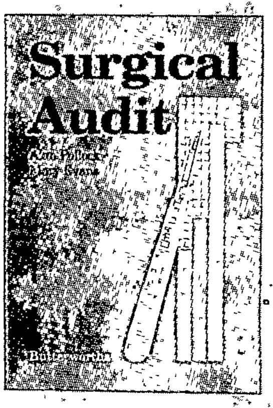

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Radiocephalic fistula in vascular access

In 1988 over 4000 patients with end stage renal failure in the United Kingdom required vascular access for haemodialysis[1]. The single most frequent reason for hospitalization of chronic haemodialysis patients is treatment or revision of their vascular access site[2]. It follows that the prerequisite for successful rehabilitation is the establishment of an arteriovenous fistula which remains patent in the long-term, allowing repeated access to the circulation with minimal morbidity. Despite the apparent simplicity of the operation, countless surgeons have spent many hours in operating theatres frustrated in their attempts to establish working fistulae. Moreover, despite apparent surgical 'innovations', such as the use of silicone rubber arteriovenous shunts, autogenous vein interposition grafts, bovine heterografts, Dacron® (Du Pont) reinforced denatured human umbilical cord vein, expanded polytetrafluoroethylene (ePTFE) grafts and indwelling silastic (Hickman) dialysis catheters, the Cimino–Brescia radiocephalic fistula first described in 1966[3], remains unquestionably the best available form of vascular access for haemodialysis because of its unequalled long-term patency rate and minimal complications.

The advantages of the wrist fistula include the convenient site of the cephalic vein for catheter insertion, its relatively long and straight course over the flat forearm musculature, its multiple venous tributaries which may themselves be used for dialysis, and the similarity in size of the cephalic vein and radial artery each of which lie in a relatively subcutaneous position. The vein must be patent throughout its length without previous thromboses or other causes of stricture. Relative disadvantages which may inhibit success include a small vein (<3 mm diameter), a diseased and narrowed radial artery and obesity resulting in inability to see the vein. Patients requiring dialysis often have diseased arteries which are calcified in association with diabetes mellitus, secondary hyperparathyroidism or various forms of vasculitis.

The great majority of patients with chronic renal failure will be suitable candidates for construction of a wrist fistula whether for primary treatment by haemodialysis or as a reserve option for those who are on peritoneal dialysis as a prelude to transplantation. Before operation, careful physical examination is vital. Firstly, the Allen test should be performed to determine patency of the radial and ulnar arteries and of the anastomosis through the palmar arch. If either vessel is occluded at the wrist or an incomplete or absent palmar arch is demonstrated, the other wrist should be used. If the abnormality is bilateral, the patient is not suitable for a wrist fistula. If the circulation is 'normal' on both sides, the wrist on the nondominant arm is chosen for the operation.

The cephalic vein normally begins in the radial part of the dorsal venous network and winds upward around the radial border of the forearm, receiving tributaries from both surfaces. Distal to the elbow, it gives off the medial cubital vein, which receives a communicating branch from the deep veins of the forearm and joins the basilic vein over the antecubital fossa. The cephalic vein then continues on the outer aspect of the upper arm and dips into the deltopectoral groove to pierce the clavipectoral fascia and empty into the axillary vein. There may be considerable variations in this course. The cephalic vein, although well developed at the wrist, may drain into a number of smaller forearm veins, a variation which results in an inadequate length of arterialized vein for repeated dialysis[4]. Preoperative evaluation should include application of a venous tourniquet just below the elbow. Gentle percussion of the vein at wrist level should then transmit a wave palpable at the antecubital level. This test confirms patency of the cephalic vein throughout the forearm[4].

The procedure can be performed under local anaesthetic (without adrenaline) on a day case basis. The skin of the forearm and hand is prepared and draped in the standard aseptic manner. Axillary or brachial block anaesthesia is unnecessary but is preferred by some because of the theoretical advantage of sympathetic block inhibiting vasospasm. A transverse incision is made through the skin and subcutaneous tissue at the level of the head of the radius. The sensory branch of the radial nerve to the thenar eminence should be identified and avoided. A proximal skin flap is elevated and the cephalic vein is exposed. This is elevated by passing a latex vessel loop or traction suture around it. The radial artery is next exposed by incising the deep fascia over the site of the radial pulse. Small posterior branches are tied in continuity and divided, thus 'freeing up' approximately 1–2 cm of artery. Small vessel loops or miniature vascular clamps are used to occlude the artery above and below the site of the anastomosis. The vein is divided distally and the proximal end is spatulated for a length of approximately 4–5 mm. The arteriotomy is made of a similar length using an 11 blade knife for incision and microvascular angled scissors

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for extension. After irrigating both vessels with heparinized saline, an end-to-side anastomosis is fashioned using 7/0 polypropylene sutures.

If the surgeon prefers, the anastomosis can be fashioned in a side-to-side manner. However, the distal venous limb should be ligated on completion of the anastomosis to obviate the complication of venous hypertension in the hand. On release of the arterial clamps, a strong pulse and thrill should be appreciable in the vein. The procedure is greatly facilitated if the surgeon employs the aid of loupe lenses. On completion, despite a palpable pulse in the vein, the absence of a thrill usually denotes a technical problem. One side of the anastomosis can be reopened, inspected for the presence of a clot or suture 'tagging' of the back wall. A small Fogarty embolectomy catheter may be passed up either vein or artery and clot removed. If all is not satisfactory the anastomosis should be refashioned. Sterioff studied[5] the function of 422 radial–cephalic fistulae in 380 patients and demonstrated that the reasons for failure are, in order of frequency: (1) technical problems at the anastomosis and positioning of the artery and vein relative to one another including rotation and angulation; (2) a sclerotic vein segment in the proximal forearm which is unrecognized preoperatively; (3) calcification of the arterial wall causing difficulty at the anastomosis, such as elevation of an intimal flap, lack of distensibility of the arterial wall, or poor flow because of proximal occlusive disease; and (4) hypotension usually associated with low blood volume from recent haemodialysis resulting in poor flow through the anastomosis.

The principle disadvantage of the arteriovenous fistula is that bleeding, haematoma formation and false aneurysm are likely to occur if the fistula is used for dialysis in the first 30 days after construction, before the vein is 'arterialized' by intimal hyperplasia. Hence the importance of early referral to the surgeon who can make plans so that the fistula is ready for use when the time comes for renal replacement therapy. Although this type of surgery lacks the glamour of more 'major' vascular procedures, for these patients a successfully fashioned primary fistula provides a critical lifeline to optimal health with minimal hospitalization and morbidity. Such procedures should not be delegated to juniors untrained in these specific techniques. Several other sites for arteriovenous fistulae are described but none measures up to the results obtained with a successful radiocephalic fistula. Prosthetic shunt materials allow the surgeon a valuable alternative for those patients in whom a primary fistula is not feasible. Their availability should not, however, diminish the importance of the primary arteriovenous fistula procedure.

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Tissue injury by free radicals and other toxic oxygen metabolites

In 1969, when McCord and Fridovich first suggested that free radical chemistry, until then a subject of interest only to the high energy physicist or the radiation biologist, might comprise an integral component of normal metabolism[1], they were not taken seriously. Today, we not only recognize that they were correct, but we encounter examples of free radical-mediated mechanisms regularly in our clinical journals. Indeed, we have recently come to realize that free radical-mediated tissue injury is a final common pathway of damage and an integral component of a wide variety of disparate pathophysiological, and even physiological processes.

A free radical is a molecule with one or more unpaired electrons in its outer orbital. This makes these species quite unstable, highly reactive and thereby toxic; the free radical tends to react rapidly with other molecules to pair the electron(s), thereby generating a more stable species. Whereas the extreme toxicity of free radicals and other toxic oxygen metabolites was once thought to make their endogenous generation by living organisms inconsistent with survival, we now know that toxic oxygen metabolites are generated continuously by a wide variety of metabolic processes throughout the cell. During oxidative phosphorylation within the mitochondrion, the production of adenosine triphosphate (ATP) is coupled to the tetravalent reduction of molecular oxygen to water. However, about 1–5 per cent of oxygen which is reduced to water 'leaks' out from this cytochrome-catalyzed pathway and undergoes non-catalytic, stepwise, univalent reduction, thereby producing a number of toxic intermediates. This continuous 'univalent leak' of reactive oxygen metabolites must be 'detoxified' by protective biochemical mechanisms within the cell to prevent injury. A number of oxidases can also generate toxic oxygen metabolites. Xanthine oxidase uses molecular oxygen as an electron acceptor, thereby producing the superoxide radical as a by-product of purine metabolism.

Several potential sources of free radicals exist within the plasma membrane of the cell. The metabolism of arachidonic acid by cyclo-oxygenase or lipoxygenase involves the generation of intermediate peroxy compounds as well as hydroxy radicals. The highly specialized NADPH oxidase system on the membrane surface of macrophages catalyzes the sudden reduction of oxygen to hydrogen peroxide and the superoxide anion. This phenomenon, termed the 'respiratory burst', accounts for more than 90 per cent of oxygen consumption by a stimulated neutrophil and is one of the major mechanisms, through the secondary generation of hypochlorous acid, by which phagocytes destroy microorganisms.

Because they are so highly reactive, free radicals may react with almost any biochemical component of the cell. Membrane lipids are particularly vulnerable to free radical-mediated lipid peroxidation, a classical chain reaction which results in extensive cell membrane injury from relatively few initiating free radicals. This can result in increased cell permeability and even cell lysis. Both structural and enzymatic proteins are susceptible to free radical-mediated denaturation. Oxygen-derived free radicals can also directly attack nucleic acids, causing base hydroxylation, cross-linking or DNA strand scission. Depending upon the degree of damage sustained, the effect may be lethal or mutagenic.

These basic, free radical-mediated reactions are important final common pathways of tissue injury in biological systems, appearing whenever the balance between free radical generation and endogenous scavenging capabilities is disrupted. For example, both the acute pulmonary toxicity and the long-term carcinogenicity of cigarette smoke are largely mediated by toxic oxygen metabolites[2].

A number of exogenous toxins act through free radical-mediated mechanisms. The acute pulmonary toxicity of bleomycin or paraquat, and the hepatotoxicity of alcohol or carbon tetrachloride are examples. Moreover, about two-thirds of the radiobiological effects of radiation are mediated by the secondary generation of such toxic metabolites of oxygen (the basis for the term 'ionizing radiation'). This explains the relative radiation resistance of hypoxic tumour cells. Indeed, both the instant deaths of those unfortunate individuals who were vaporized by the nuclear detonation at Hiroshima, and the malignancies that appeared years later in survivors were largely free radical-mediated.

Because reactive oxygen metabolites are generated continuously within the cell, a number of endogenous mechanisms have evolved by which organisms can prevent or limit injury. For example, the mitochondrial cytochrome oxidase system consumes most of the oxygen available within the cell, preventing 95–99 per cent of it from forming toxic metabolites. In fact, this biochemical mechanism appears to have evolved initially as a means of protection against the toxicity of ambient atmospheric oxygen, and was only secondarily exploited by natural selection as a very efficient source of energy. The enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase also catalyze reactions which detoxify toxic oxygen metabolites. The fact that the amino acid sequences of endogenous scavengers such as SOD have been highly conserved throughout the evolution of eukaryotic and even prokaryotic species supports the concept that the ability to detoxify oxygen and its reactive metabolites is essential for survival in an aerobic environment.

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The role of toxic oxygen metabolites in ischaemia/reperfusion injury is particularly illustrative of a free radical-mediated mechanism of damage. In this injury, hypoxanthine and xanthine accumulate during ischaemia from the catabolism of ATP. At the same time, ischaemia mediates the conversion of the non-radical generating enzyme xanthine dehydrogenase to the radical generating form, xanthine oxidase. When oxygen is reintroduced at reperfusion, superoxide (O_2^-) is generated rapidly, initiating a cascade of toxic oxygen metabolites which causes tissue injury. The entire xanthine oxidase-based free radical-generating system is present and operative in the endothelial cell itself[3]. We have proposed that this endothelial cell trigger mechanism is a ubiquitous initiator of free radical-mediated reperfusion injury. In many cases the secondary activation of neutrophils, which themselves generate toxic oxygen metabolites as well as toxic proteases, amplifies this insult to a diffuse, microvascular injury, resulting in a non-reflow phenomenon. This mechanism, first described by Granger and his colleagues in the cat small intestine[4], has been found to operate in the stomach, pancreas, liver, heart, lung, kidney, skin, skeletal muscle, and central nervous system. In each of these organs a substantial proportion of the injury sustained as a consequence of ischaemia is generated by this mechanism at the time of reperfusion. Theoretically, injury such as that sustained by the brain as a consequence of cardiac arrest might still be amenable to prevention at the initiation of cardiopulmonary resuscitation. In each case, however, the reperfusion component is dominant only within certain time intervals[5]. This therapeutic window appears to limit the effectiveness of pharmacological inhibition of free radical-mediated reperfusion injury. Nevertheless, in large, carefully designed clinical trials of the use of free radical scavengers to prevent early renal failure in patients receiving cold-ischaemia-preserved cadaveric renal transplants, a dramatic effect was demonstrated in those patients in the SOD group whose grafts had been preserved for ischaemic periods falling within this window[6].

The ubiquity of toxic oxygen metabolites in biological systems underlines the fundamental role which free radicals play as a final common pathway of tissue injury in a wide variety of disease states. An understanding of these free radical-mediated mechanisms is essential in order to comprehend fully the basic workings of the cell. For example, it is impossible to understand the effects of prostaglandins and leukotrienes without taking free radicals into account. Fortunately, free radical toxicity may be controlled easily, through a number of pharmacological means, most of which are quite non-toxic[7]. Although there has been a great deal of publicity surrounding the use of recombinant human SOD for the treatment of reperfusion injury, in most cases an equivalent effect can be obtained with the xanthine oxidase inhibitor allopurinol, a safe and well-established drug that has been on the market so long for the treatment of hyperuricaemia that it is no longer patent-protected. On the other hand, in some organs, such as the heart, the therapeutic window appears to be so small that the potential for benefit has been disappointing[8]. Unless clinical trials are designed to account for patient heterogeneity by stratifying the time of ischaemia in order to define the therapeutic window, they are unlikely to be enlightening.

As implied above, free radical biology, like many new fields, has suffered some growing pains, as well-justified enthusiasm and sometimes hyperbole have not always generated thoughtfully- designed studies. Nevertheless, the ubiquity of free radical toxicity and the existing methods for pharmacological control make it quite likely that free radical ablation will become a routine component of our clinical armamentarium in the new decade.

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Stercoral perforation of the colon

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Stercoral perforation of the colon is rare. The 64 reported cases are reviewed to define the syndrome of stercoral perforation, and to facilitate accurate diagnosis and treatment. Features of localized or generalized peritonitis were universal; however, only 11 per cent were correctly diagnosed before operation. Recognition that the disease involves a segment of colon rather than only the focal point of perforation is essential to adequate surgical treatment. It is postulated that this is the reason for the higher postoperative mortality following closure of the perforation and proximal colostomy (57 per cent) or exteriorization alone (43 per cent), compared with resection of the diseased segment and exteriorization (32 per cent). Resection and exteriorization is therefore the treatment of choice is most situations.

Keywords: Stercoral perforation, colonic perforation, peritonitis, intraoperative colonic lavage, mortality

Stercoral perforation of the colon is rarely reported in the surgical literature. Similarly, idiopathic and spontaneous perforations are infrequently reported; however, they have often been grouped together with stercoral perforation, resulting in confusion. The purpose of this review is clearly to define the syndrome of stercoral perforation, to distinguish it from other entities, and to facilitate accurate diagnosis and treatment. Hence it aims to reduce the high mortality of this condition.

Since the first report of stercoral perforation to the Pathological Society of London by Berry in 1894[1], only 66 cases have been reported in the literature[2–36]. However, this number is variably quoted due to lack of a consistent definition of stercoral, idiopathic and spontaneous perforations of the colon. There is little disagreement regarding the proper definition of stercoral perforation, namely 'perforation of the bowel due to pressure necrosis from faecal masses'. However, stercoral perforation must be carefully distinguished from idiopathic and spontaneous perforation as a number of features including chronic constipation and scybala are common to all three conditions.

In this review the definition of Noussias[37] has been adopted where the term 'idiopathic perforation' is reserved for those cases in which no demonstrable pathology is present to account for the perforation. Many published reports of spontaneous perforation are thus examples of idiopathic perforation[38–42]. Further, Brearley[4] has suggested that the term 'spontaneous perforation' implies a perforation that is not due to external trauma. This seems logical as there must exist a point in the natural history when a carcinoma, complicated diverticulitis or, indeed, a stercoral ulcer as a development in its pathology undergoes spontaneous perforation. Hence, for the purpose of this review the term 'idiopathic perforation' is used, and all other perforations are considered secondary to an underlying pathology, regardless of whether this occurred spontaneously or due to trauma. Stercoral perforation hence falls into this second category. This approach was adopted by Kasahara *et al.* in a large review of idiopathic perforation from Japan[43].

An analogous situation exists in the oesophagus where the confusion associated with the condition of spontaneous rupture is overcome by the use of an eponymous name for the syndrome of idiopathic rupture, namely Boerhaave's syndrome[44]. While eponyms are in general to be deprecated, it would seem this could clarify the situation in the colon if all idiopathic perforations were reported as examples of Huntley's syndrome[45], who first described the condition, hence allowing the confusing term 'spontaneous perforation' to be deleted.

It must be stated, however, that while the definitions adopted in this review have been used by others[15,28,38,42,43], the majority of authors have retained the term 'spontaneous perforation'[46].

Abella and Fernandez[47] defined a 'faecaloma' or 'stercoroma' as a localized accumulation of faecal matter which stagnates and increases in volume until the colon becomes deformed. When such a mass is small, firm and has a smooth surface it is termed a 'stercolith' or 'enterolith'. Cid *et al.*[48] furthered this definition by stating that a 'faecalòma' is harder in consistency than a faecal impaction, often laminated, usually radio-opaque and found most often in the rectum, but also in the sigmoid colon

Implicit in these definitions is the concept of a localized hard faecal mass, usually of a diameter equal to or greater than the colon, with characteristics similar to those of a tumour However, the degree of inspissation and calcification, and the size of the mass are ill-defined. Therefore, in this review the terms faecal or stercoraceous mass, 'faecaloma', 'stercoroma', and scybalum are taken to be synonymous and, for clarity of presentation, the last term has been used throughout.

Patients and methods

Utilizing these definitions, the literature has been reviewed and demographic, operative, pathological and outcome details have been recorded to characterize the condition of stercoral perforation of the colon, occurring in the absence of other associated colonic pathology Excluded from the review is the general problem of stercoral ulceration without perforation, as are the much commoner stercoral ulcers proximal to an obstructing lesion of the colon Stercoral perforation has also been reported in the terminal ileum[19,49], but this review is confined to the colon

Three patients with stercoral perforation in association with additional colonic pathology[14,30] were therefore excluded, as were five patients with colonic perforation caused by 'coprostasis'[50] because there was insufficient information to categorize them as either stercoral or idiopathic perforations As a result, 64 cases are analysed in this review

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Results

Diagnosis

Of the total of 64 cases reviewed, the median age was 60 years, with a range of 16 to 89 years. There were 29 (45 per cent) men and 35 (55 per cent) women. Fifteen (23 per cent) patients came from a chronic nursing home or similar environment.

Only 39 (61 per cent) admitted to a long history of chronic constipation preceding the stercoral perforation. Ingestion of the following substances may have predisposed patients to constipation: ten patients were taking antacids containing aluminium hydroxide[4,7,19,20,22,31,36]; five were taking regular codeine[9,27,29,34]; one patient was a narcotic addict[16]; two were taking a self-prescribed clay mixture[19]; five patients were taking amitriptyline or other constipating sedatives[10,12,25,26,31]; and one patient exhibited a pica for paper[21]. Five patients were in chronic renal failure[19,22,26,32], and three had undergone renal transplantation[20].

A diagnosis of an acute abdomen was readily made with local peritonitis in 13 patients (20 per cent), and generalized peritonitis in the remaining 51 (80 per cent). An abdominal mass was palpable in 15 patients, and four patients had a large faecal mass palpable on rectal examination. All masses were thought to represent scybala within the bowel Despite the universal presence of peritonitis the correct diagnosis was only made before surgery in seven patients (11 per cent).

Of 43 patients subjected to plain radiography of the chest and abdomen, 23 patients (53 per cent) had a pneumoperitoneum, and one patient had a pneumomediastinum[35]. In nine patients (21 per cent) a calcified scybalum was demonstrated and a further 13 patients (30 per cent) had evidence of marked faecal loading.

Of three patients who underwent barium enema examination, one showed a mass lesion in the caecum[17], one showed an obstruction at the sigmoid level[22] and one showed a posterior perforation in the descending colon[35]. However, none of these examinations contributed to a correct preoperative diagnosis. In one patient a Gastrografin® (Schering Health Care Ltd., Burgess Hill, UK) enema revealed scybala in the sigmoid, and enabled a correct preoperative diagnosis of stercoral perforation to be made[31].

Operative and autopsy findings

In 57 patients where the site of perforation was documented, the most common site was the sigmoid colon (47 per cent). Next commonest was the rectosigmoid (30 per cent) followed by the caecum (9 per cent), transverse colon (7 per cent), descending colon (5 per cent) and splenic flexure (2 per cent). The perforation was single in 79 per cent and multiple in the remainder. Where documented, all perforations except one[35] occurred on the antimesenteric border of the colon. The colon was loaded with multiple scybala in 40 patients (63 per cent). In one case the perforation occurred proximal to an end transverse colostomy; however, this occurred at least 18 years after establishment of the colostomy[28].

Treatment

Twelve patients (19 per cent) were managed conservatively and the diagnosis of stercoral perforation was established at post-mortem examination. The remaining 52 patients were submitted to laparotomy. Resection of the diseased colon and exteriorization of the proximal colon and conversion to a Hartmann's or a distal mucous fistula was performed in 25 patients (48 per cent). The next commonest procedure was exteriorization of the perforation without resection in 14 patients (27 per cent) followed by closure of the perforation with a proximal colostomy in seven patients (13 per cent), resection and primary anastomosis in four patients (8 per cent) and resection, primary anastomosis and proximal colostomy in two patients (4 per cent). Before 1975, of 32 patients submitted to laparotomy, 53 per cent underwent exteriorization of the perforation alone, or closure of the perforation with proximal colostomy, whereas 31 per cent underwent resection and exteriorization. This is in contrast to the period since 1975 where 75 per cent of the 20 patients operated upon underwent resection and exteriorization. The operative procedure performed could not be related to the patient's general condition before laparotomy.

Pathology

Where available for pathological examination, the gross resected specimens showed features of colonic loading with scybala, fibrinous exudate, and external evidence of inflammation, necrosis and friability. The mucosa was ulcerated in a geographical pattern, with the perforations occurring centrally in the ulcerated area, with the shape being either round or ovoid.

Several reports noted the presence of faecal material both within and through the bowel wall in multiple sites separate from the main site of perforation, which was itself often plugged by a large scybalum[17]

Mortality

Of the 52 patients operated upon for stercoral perforation, 18 died after surgery (35 per cent). If those managed conservatively are included, the rate increases to 47 per cent. However, of the 12 patients managed conservatively, 11 were in the period before 1975. When mortality is analysed according to type of operative treatment, marked differences are noted. Closure of the perforation with proximal colostomy resulted in the death of four patients (57 per cent), exteriorization of the perforation alone in the death of six (43 per cent), and resection and exteriorization in the death of eight (32 per cent) There was no difference in the mortality rate before and after 1975. Analysis of disease-related mortality revealed that all four deaths after closure of the perforation and proximal colostomy were due to uncontrolled sepsis, as were five of the six deaths following exteriorization alone. However, after resection and exteriorization, only three of eight deaths were attributed to sepsis; and only one of these occurred after 1975.

Discussion

Incidence

Accounts of stercoral perforation of the colon rarely appear in the literature. We have identified only 64 cases from the literature for the 95 years from 1894 to 1989 This is surprising in view of the finding of Grinvalsky and Bowerman[5] of a 4·6 per cent incidence of stercoral ulcer in 175 autopsies performed over a 12-month period. In marked contast is the finding of a single case in 2500 autopsies performed on psychiatric and mentally defective patients[25]. Lal and Brown[10] reviewed 375 consecutive autopsies and found only one case of peritonitis due to stercoral perforation. Hence it is difficult to determine precisely the true incidence of stercoral perforation. An explanation for the rarity of the disease is not apparent, but almost certainly it is under-reported[13,16].

Aetiological factors

The literature identifies chronic constipation as a major predisposing factor to stercoral ulceration[13,28], being documented in 61 per cent of patients. It is therefore surprising that the condition is not more common, considering the prevalence of chronic constipation in Western society. In addition, considering the prevalence of narcotic addiction, it is surprising only one related case has been reported. Furthermore, faecal impaction is recognized as a commonplace occurrence, yet its complication of stercoral ulceration and perforation it is uncommonly reported.

An interesting association is that of colonic perforation with renal transplantation, and many factors are thought to contribute to the pathogenesis[20,22]. This series includes three cases of stercoral perforation following renal transplantation, all of whom were on immunosuppressive agents (including steroids), which may in themselves increase the likelihood of colonic perforation[20]. Constipation and faecal impaction is common following renal transplantation[51] and may lead to perforation. Further, laparotomy has occasionally been necessary to remove the impaction[52].

Whatever the associated factors it would appear that in order to develop stercoral ulceration, the presence of a scybalum is necessary to initiate the ischaemic pressure necrosis. Factors responsible for formation of scybala include all those associated with the production of constipation identified in this review. In addition mechanical obstruction, motility disorders, megacolon, decreased mucus production, a prior barium enema, and foreign bodies or gallstones acting as a nucleus may all predispose to scybalum formation[8,12,53]. Scybala may be present for months; even up to 5 years[13,51]. Furthermore, although a scybalum will usually produce symptoms, apparently normal bowel function may be present[13].

Diagnosis

Contrary to common anecdotal beliefs, stercoral perforation does not necessarily occur in the geriatric population, nor is a chronic institutionalized environment a common concomitant factor (23 per cent)[13,46].

All patients had features of peritonitis, and hence it could be argued that the need for urgent laparotomy for an acute abdominal condition was self-evident. Therefore attempts to establish a diagnosis before surgery are perhaps of academic interest alone[13,46]. However, it is clear from the collective series that a number of cases were diagnosed at post-mortem examination or were operated upon in a moribund condition. Hence, it would be valuable to make an early correct diagnosis as the best treatment is undoubtedly early surgery.

Although no characteristic presentation can be ascribed to a patient with stercoral perforation, it would appear that in a patient with a long history of constipation who presents with peritonitis, who in addition has a palpable abdominal mass and plain abdominal radiographic findings of pneumoperitoneum, faecal loading or calcified scybala, a diagnosis of stercoral perforation should be strongly considered.

Contrast enema studies have been performed too infrequently to establish their value. However, in view of the similarities between stercoral and diverticular perforations, and the trend in some centres in the latter to pursue conservative treatment[54], a positive diagnosis of diverticular disease on contrast examination at an early stage is mandatory if cases of stercoral perforation are not to be missed. This is of great importance because, whereas in selected cases of perforated diverticulitis a conservative approach is appropriate, this is not so in stercoral perforation where surgical intervention is mandatory.

Pathology

Two varieties of stercoral ulceration should be distinguished. First, that occurring at some distance proximal to an obstructing lesion, and secondly, stercoral ulceration occurring due to direct pressure necrosis from a scybalum occurring as a primary event. Textbooks of general and surgical pathology emphasize the role of obstruction in the causation of stercoral ulceration[55]. Anderson[56] states that stercoral ulcers develop in the segment above the obstruction, owing to the irritation of the hard scybalous masses which collect there. Rubin[57], however, includes ulceration of the rectosigmoid consequent on faecal impaction under the heading of stercoral ulceration, and lists the complications as massive rectal bleeding, perforation and chronic anaemia due to chronic blood loss

Grinvalsky and Bowerman[5] characterized the pathology of stercoral ulcers in 1959. The lesion is an ischaemic pressure necrosis due to hard scybala producing irregular, geographically outlined ulcers which conform to the contour of the impacted scybala. The ulcers are depressed below the mucosal level, often multiple and histologically show ischaemic pressure necrosis and an inflammatory reaction. A rounded or ovoid perforation may occur in the centre of the ulcer where thinning is maximal This is in marked contrast to an idiopathic perforation where there is a linear tear, without inflammation or necrosis[42,46]

With respect to pathophysiology it is postulated that, as the bowel distends due to the scybalum, the intraluminal pressure generated becomes greater than the capillary perfusion pressure within the bowel wall, particularly on the antimesenteric border, leading first to ulceration and then to subsequent perforation[4,32] It seems likely that the watershed region of blood supply on the antimesenteric border of the colon where anastomoses between the vasa recta longa are poor is the explanation for the stercoral mass exerting its greatest pressure necrosis at this site[58]. Where recorded the vast majority of perforations occurred on the antimesenteric border.

Overall 77 per cent of stercoral perforations occurred in the sigmoid and rectosigmoid segments of the colon with 47 per cent occurring in the sigmoid colon itself. In view of the proposed pathophysiology, several reasons for this distribution seem possible. First, faecal content becomes progressively dehydrated as it passes along the colon, therefore scybala would be more likely to form in the distal colon[17]. Secondly, the colon distal to the mid-transverse colon has a relatively poor blood supply, especially in the elderly, as evidenced by the occurrence of ischaemic colitis in this situation[59]. Hence scybala would be more likely to exert an ischaemic effect in the distal colon[29]. Thirdly, the sigmoid and rectosigmoid have the narrowest diameter of the colon and, in addition, generate high intraluminal pressures of between 5 and 100 cmH_2O within them[60]. For both reasons a scybalum would be most likely to cause ulceration in the sigmoid and rectosigmoid as opposed to other areas of the colon[14]. The suggestion that the sigmoid colon lacks available space to distend into and hence predisposes to stercoral ulceration due to an expanding scybalum within it seems improbable[28].

Treatment

While a number of similarities exist between the condition of perforated diverticulitis and stercoral perforation, there are several important differences that influence treatment. First, the stercoral perforations are multiple in up to 21 per cent of cases and the stercoral ulceration itself is almost always multiple. Second, in 63 per cent of patients the proximal colon is loaded with multiple scybala. Third, the inflammatory and necrotic pathological process involves a segment of colon, rather than being confined to the area of perforation[13,31] Fourth, stercoral perforations are almost invariably free and open, although to some extent plugged by a scybalum, hence there is no possibility of spontaneous resolution with conservative treatment as may occur in perforated diverticulitis[54].

Logically, therefore, resection of the diseased segment of bowel and exteriorization, rather than exteriorization of the perforation alone, or closure of the perforation with proximal colostomy, where the diseased segment remains partially or wholly within the peritoneal cavity, would seem the most appropriate operation[13,29,32]. This is confirmed by the mortality of 32 per cent after resection and exteriorization compared with 43 per cent after exteriorization of the perforation alone, and 57 per cent following closure of the perforation with proximal colostomy. Furthermore, following procedures not involving resection, mortality was attributed to uncontrolled sepsis in 90 per cent, whereas after resection and exteriorization sepsis was responsible for 38 per cent of the mortality. No correlation between the general condition of the patient and the operative procedure performed is identifiable from the literature. However, since 1975 resection and exteriorization was the commonest procedure (75 per cent). Although there was no difference in overall mortality during the two periods, the disease-related mortality was substantially lower after 1975. It is likely that this is due not only to substantial improvements in antibiotic and supportive therapy, but also to the more frequent use of resection in the later period Similar trends in emergency surgery for diverticular disease have been reported[61].

Of four patients undergoing resection and primary anastomosis, three were suffering from caecal perforations. There was no mortality in this group, hence resection and primary anastomosis for right-sided perforations seems feasible[17,28]. However, for left-sided lesions where gross contamination and an unprepared bowel co-exist in combination with a moribund patient, this approach seems inappropriate[26]

In contrast to similar situations in diverticular disease, mobilization of the left colon presents few problems, hence in most instances exteriorization alone or in combination with resection will be possible. However, for the reasons outlined, resection and exteriorization should be the preferred option. A further advantage of this technique is that it enables a pathological diagnosis to be reached on the resected specimen. This would be of advantage in allowing the true incidence of the condition to be documented

The well established principles of treatment for generalized peritonitis are applicable to that due to stercoral perforation. These principles include adequate resuscitation, antibiotic therapy, early operation, surgical eradication of the source of sepsis, and intraoperative peritoneal lavage[32,62]

Stercoral perforation proximal to an end colostomy has not previously been reported as a postoperative complication. We have recently managed two such cases, both occurring in the early postoperative period. In both cases marked faecal loading was present proximal to the site of perforation. In one the stercoral perforation was recurrent, occurring proximal to an end colostomy, where it seems likely that the full extent of the diseased colon was not resected at the original operation. It has always been considered that a terminal defunctioning colostomy, in contrast to an intraperitoneal anastomosis, protects the patient from the dangers of intraperitoneal leakage, as the faecal stream is diverted from, and thus cannot leak into, the peritoneal cavity. Hughes *et al.*[63] mention faecal impaction as a cause of colostomy retraction, but do not list stercoral perforation as a complication of an end colostomy.

It is notable from this review that only the reports of Bauer *et al.*[12] and Carter and Kirkpatrick[13] documented or made recommendations as to the most appropriate method of dealing with the loaded proximal colon. For the reasons outlined above, and in view of the recurrent stercoral perforation now reported, management of the proximal colon should be a definitive part of the operative management of stercoral perforation. Goligher[64] suggests three methods to deal with the problem of faecal loading. First a Hartmann's type procedure may be performed. In the case of stercoral perforation, this procedure alone will not guarantee that the problem will not occur or recur. Second, he suggests emptying as much faeces as possible into the segment of bowel to be resected. However this is always an incomplete procedure and in a colon loaded with scybala is unlikely to be effective. Third, intraoperative orthograde colonic irrigation may be undertaken to clear the proximal colon[65]. This is now an established technique[66] and it is suggested that the occurrence of stercoral perforation proximal to an end colostomy extends the indications for intraoperative orthograde colonic lavage to avoid this postoperative complication

The overall postoperative mortality of 35 per cent in this collected series of patients with stercoral perforation is much higher than rates of between 12 per cent and 22 per cent obtained in comparable situations in emergency surgery for diverticular disease[61]. Clearly this points to a need for more accurate and early diagnosis, and an understanding that prompt surgical intervention is the management of choice

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Surgical strategy for early gastric cancer

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The diagnostic and therapeutic options in early gastric cancer are reviewed. In Japan, the rate of detection of early gastric cancers has increased so that minute gastric cancers can now be identified as a result of advances in diagnostic methods. The results of histopathological staging of a large number of resected specimens have led to three surgical options based on size and depth of the primary lesion, namely classical R_2 resection, radical resection with limited lymphadenectomy and endoscopic surgery.

Keywords: Early gastric cancer, lymph node metastasis, radical operation with limited lymphadenectomy, endoscopic surgery

The prognosis in gastric cancer has improved markedly in Japan during the last three decades. The most important reason is that the rate of early detection has increased owing to improved radiography and endoscopy. Recent figures show that in most Japanese hospitals 30–40 per cent of all gastric malignancies are detected at an early stage[1–4] The other reason for improved prognosis is based on better staging following the general rules for the Gastric Cancer Study in Surgery and Pathology established by the Japanese Research Society in 1962. This has provided a large database resulting in a greater understanding of the lymphatic spread of early gastric cancer and allowing a more rational approach to lymphadenectomy[5,6]

The prognosis after curative gastrectomy for early gastric cancer is very favourable, the 5- and 10-year survival rates being over 90 per cent and 80 per cent respectively in Japan[1,2,6–13] When early gastric cancers are divided into mucosal and submucosal cancers, the prognosis for mucosal cancers is much better. The Japanese definitions and macroscopic classification of early gastric cancer are widely used in Western countries. In Europe and North America 5-year survival rates are also over 90 per cent, even though the numbers are small[14–22]. Thus, the favourable prognosis of early gastric cancer holds world-wide and emphasizes the importance of early detection of cancers. While the rate of lymph node metastasis for mucosal cancers is low (about 3 per cent), that for submucosal cancers is about 20 per cent. Metastasis to sites other than lymph nodes is very rare in patients with early gastric cancer, so that lymph node dissection in combination with complete resection of the lesion results in cure for most patients. For this reason lymphadenectomy can be modified, unlike the situation in advanced gastric cancer where the R_2 operation (complete dissection of the group 2 lymph nodes) has been the standard operation in Japan for over three decades. In early gastric cancer the rate of lymph node metastasis depends not only on the depth of the primary lesion but also on sex, age, histological type and tumour morphology.

This paper reviews the diagnostic and therapeutic methods that are currently used in Japan and Western countries, and attempts to define optimum therapy.

Our clinicopathological data were evaluated on the basis of the general rules for the Gastric Cancer Study in Surgery and Pathology[23] where the regional lymph nodes are numbered according to their anatomical location (*Table 1*). They were also classified into groups 1, 2 and 3 according to the location of cancer in the stomach. Gastric resection based on lymph node clearance was classified as follows: R_0, gastric resection including the incomplete removal of group 1 lymph nodes; R_1, gastric resection including the complete removal of group 1 lymph nodes alone; R_2, gastric resection including the complete removal of groups 1 and 2 lymph nodes; and R_3, gastric resection including the complete removal of groups 1, 2 and 3 lymph nodes. Histopathologically, papillary adenocarcinoma and tubular adenocarcinoma were grouped together as differentiated, whereas poorly differentiated adenocarcinoma and signet-ring cell carcinomas were regarded as undifferentiated adenocarcinoma. Macroscopic or descriptive classification of early gastric cancer follows that of the Japanese Society for Gastroenterological Endoscopy[24] (*Figure 1*).

Diagnosis of early gastric cancer

An accurate preoperative diagnosis is essential. The first step is to determine whether the cancer is early or advanced. Early gastric cancers should be subdivided according to (1) whether the malignancy is confined to the mucosa or has invaded the submucosa; (2) its macroscopic appearance; (3) whether it is multifocal; and (4) its histological type[25–28]. Assessment is made by radiography and endoscopy. In Western countries endoscopy is generally regarded as more sensitive than radiography[7–20,29,30], hence endoscopy is the diagnostic method of first choice. With endoscopy, the rate of detection of early gastric cancers has increased to about 15 per cent[15–17,20,31]. On the other hand, some Japanese reports indicate that with improved photographic methods and double contrast radiography, there is no difference in the diagnostic accuracy of the two techniques[32,33].

Table 1 *Grouping and lymph node designation used in the Gastric Cancer Study*

	Location of cancer		
Group	Lower third	Middle third	Upper third
1 (N_1)	3, 4, 5, 6	1, 3, 4, 5, 6	1, 2, 3, 4
2 (N_2)	1, 7, 8, 9	2, 7, 8, 9, 10, 11	5, 6, 7, 8, 9, 10, 11
3 (N_3)	2, 10, 11, 12, 13, 14	12, 13, 14	12, 13, 14, 110, 111

Regional lymph nodes of the stomach: 1, right paracardial; 2, left paracardial; 3, lesser curvature; 4, greater curvature, 5, suprapyloric; 6, infrapyloric; 7, left gastric artery, 8, common hepatic artery; 9, coeliac artery; 10, splenic hilus; 11, splenic artery, 12, hepatic pedicle; 13, retropancreatic; 14, mesenteric root; 110, lower thoracic para-oesophageal; 111, diaphragmatic

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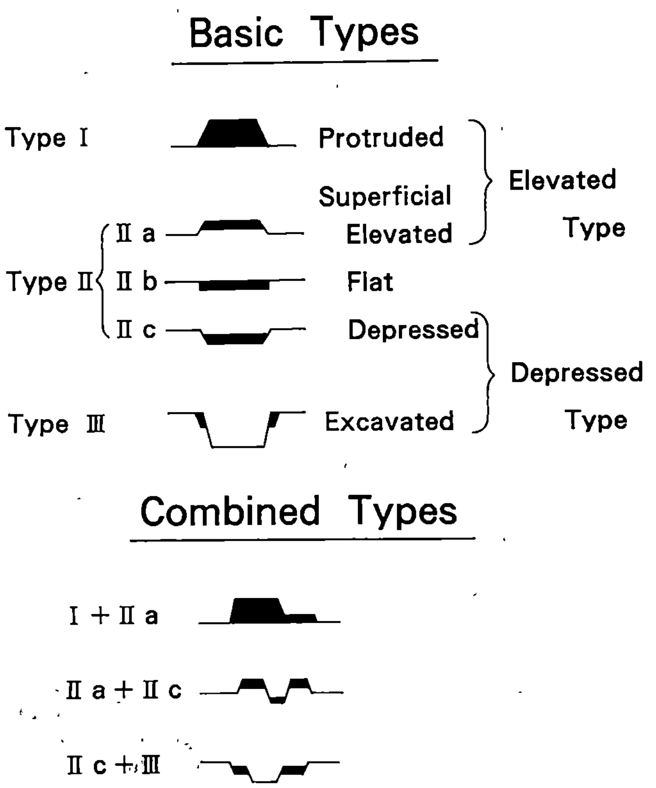

Figure 1 *Macroscopic classification of early gastric cancer*

Even though endoscopy is observer-dependent, newer developments have made this approach more informative. These advances include dye spraying methods[34,35], magnified endoscopy[36,37], electronic endoscopy[38–41] and endoscopic ultrasonography[42–44]. These improvements in diagnostic techniques have been associated with an increase in the numbers of mucosal, depressed and small (less than 2 cm diameter) cancers among early gastric cancers[4,6].

While early gastric cancer can be differentiated from advanced gastric cancer in 80–90 per cent of cases[45–47], the preoperative differentiation between mucosal and submucosal cancers is often not achieved even with endoscopic endoluminal ultrasound. The accuracy in elevated lesions (I and IIa) is high[45–48] but the preoperative diagnosis of depressed lesions (IIc and III), especially those associated with ulceration, is poor[46–49]. Despite a high reputation for determining the depth of invasion, endoluminal ultrasound is accurate in only 70–80 per cent of of cases of ulcerating early gastric cancer because of the degree of fibrosis in the submucosa and muscular propria[43,44,50,51]. Furthermore, current endoluminal ultrasound probes require that the patient drinks a considerable volume of degassed water, endoscopic visualization is often suboptimal because the optics on the endoscopes are poor, and the endoscopes themselves have a wide diameter making patient co-operation poor. Further improvements in the development and design of these devices is needed before their full benefit can be realized.

Preoperative diagnosis of metastatic lymph nodes

The preoperative diagnosis of lymph node metastasis used to rely on examination such as computed tomography (CT)[52–55] and ultrasonography[56]. These techniques visualize only enlarged lymph nodes but do not differentiate hyperplasia from neoplasia. In early gastric cancer lymphatic metastases are largely confined to the perigastric lymph nodes which are usually small. Attempts to improve the accuracy of preoperative lymph node involvement include immunolocalization with an isotope, endoscopic lymphography[57], endoluminal ultrasound[44,58] and dynamic CT[52]. In endoscopic lymphography[57] contrast medium is injected into the submucosa or muscle layer near the tumour at endoscopy followed by plain radiographic examination. Non-metastatic lymph nodes are usually less than 5 mm in size and have a finely nodular appearance. Metastatic lymph nodes are usually visualized as filling defects, diffuse lymphatic swellings, areas of uptake with marginal irregularity and other abnormalities.

Endoscopic ultrasonography may incorporate a 10 per cent oil-in-water emulsion administered orally[58]. This technique allows visualization of the perigastric lymph nodes 2–3 h later. The ultrasonographic visualization rate of lymph nodes surrounding the gastric wall was 69 per cent for nodes over 3 mm in diameter and 76 per cent in nodes exceeding 5 mm in diameter. Uninvolved lymph nodes were characterized by echo enhancement at their margin and inside the node after the administration of the emulsion. By contrast, metastatic lymph nodes showed no enhancement in spite of administration of the emulsion. The accuracy of diagnosis of lymph node metastasis by endoluminal ultrasound after administration of the emulsion had a sensitivity of 92 per cent and specificity of 100 per cent in lymph nodes over 3 mm diameter.

While there are many reports[59,60] on the use of dynamic CT[61], few studies have evaluated the accuracy of the technique for the diagnosis of metastatic lymph nodes. Ozaki[52] compared dynamic CT with plain CT for the diagnosis of lymph nodes in patients with gastric cancer and found that the sensitivity rate for localization by dynamic CT was slightly higher (92 per cent) than that by plain CT (88·5 per cent). Furthermore, they divided the visualized lymph nodes into enhanced and non-enhanced types and reported that 81·5 per cent of enhanced lymph nodes were non-malignant, whereas 98 per cent of non-enhanced lymph nodes were metastatic. Although the diagnostic accuracy of CT for lymph node staging of gastric cancer has improved, there are regions which are difficult to visualize clearly.

With recent improvement in diagnostic techniques, the rate of detection of early gastric cancers has increased annually, being over 50 per cent in some Japanese hospitals.

What is the optimum operation for gastric cancer?

In Japan, the principal surgical procedure for early gastric cancer is the R_2 resection with complete excision of groups 1 and 2 lymph nodes. The reason for this approach is that some patients with early gastric cancer show metastasis to the group 2 lymph nodes. Furthermore, accurate intraoperative determination of the presence or absence of lymph node metastasis is very difficult[62,63]. Unlike advanced cancer, haematogenous and disseminated metastases from early cancer are so rare that complete dissection of lymph nodes results in curative resection, with a favourable prognosis.

The rate of lymph node metastasis in early gastric cancer is low for mucosal cancers (0·6–11 per cent), but much higher for submucosal cancers (14·2–26·8 per cent)[1–4,9,47,48 64–66]. The rate of metastasis to group 1 lymph nodes was reported to be 0·7–4·7 per cent for mucosal cancers and 10·6–18·9 per cent for submucosal cancers. The rates of metastasis to group 2 lymph nodes were lower than those to group 1 lymph nodes being 0–2·4 per cent for mucosal cancers and 2·3–8·9 per cent for submucosal cancers. Metastasis to groups 3 or 4 lymph nodes may also occur but only in a very small number of patients[2–4,9,65,66]. Since lymphatic metastases are predicted to occur in only 3 per cent of mucosal cancers and about 20 per cent of submucosal cancers, the conventional view that the R_2 operation should be the standard surgical procedure may be questioned. It might be argued that a selective policy should be adopted depending on the depth of the primary. Suzuki *et al.*[2] compared the extent of lymph node dissection with survival rates. In the group without lymph node metastases there was no significant difference in survival rates according to extent of lymphadenectomy. In the group with lymph node metastases the results of R_2 resection were significantly higher at 5–10 years than the R_1 operation[2].

There are few papers from Europe or North America with reference to lymph node clearance which can be compared with the Japanese data. However, Ribichini *et al.*[16] and Fass and Schumpelick[31] considered that the R_2 operation was necessary because of the incidence of metastasis in group 2 lymph nodes

In view of the immunological function of lymph nodes[67–70] and the very favourable prognosis of early gastric carcinoma, a more limited lymphadectomy is being used more frequently[9,46,47,65,71–73]. However, the main dilemma lies in staging the depth of the primary tumour[12,74–76] since radical surgery would be indicated in many submucosal early gastric cancers[12,74–76] Limited lymphadenectomy is more desirable for elderly high-risk patients

Limited surgery[9,47,73] is defined as gastrectomy involving wide excision of the primary lesion while minimizing metabolic sequelae. There are no available guidelines for determining the extent of the gastrectomy Limited surgery should probably not be performed unless the extent of the lesion and exclusion of a second primary can be assured. Furthermore, limited resection can only be justified if lymph node status is known. If the carcinoma cannot be accurately staged and the patient is fit, it is probably advisable to use the R_2 resection.

Low-risk factors for lymph node metastasis are cancers confined to the mucosa, the elevated type I and IIa lesions, small cancers and well differentiated adenocarcinoma[2,46,48,64,66,77,78]. For these types of early gastric cancer lymph node dissection can probably be limited to the R_1 operation. Some hospitals are already performing limited surgery for these groups[47,72], a policy that is expected to be used more widely as increasing numbers of patients with favourable early gastric cancer are picked up by preoperative screening.

Lymph node metastases are common in patients with submucosal or elevated early gastric cancer, particularly if they are 4 cm or more in diameter and are poorly differentiated with vascular invasion[1,2,4,9,12,64,65]. Women under 50 years tend to have unfavourable early gastric cancer[2]. In such patients the R_2 or R_3 operation, as for advanced cancers would be advised. The rate of recurrence following curative resection for early gastric cancers is very low but is higher for submucosal cancers (2·5–5·7 per cent) than for mucosal cancers (0·4–1·4 per cent)[7,9,66,79,80]. Recurrence is usually haematogenous, and the most frequent site is the liver[4,7,9,11,46,47,66,79–81]. Lymph node, bone, pulmonary and peritoneal metastases have been also reported[4,9,46,79–81]. Most recurrences occur within 5 years of operation[7,12,80,81].

Early gastric cancers which are most likely to recur are the IIa + IIc or elevated submucosal cancers, well differentiated tumours, those positive for lymph node metastasis or those in which there is vascular invasion[2,10–12,47,66,79–81]. The prognosis for aneuploid early gastric tumours was significantly worse than that for diploid tumours[82–84]

Surprisingly, differentiated early gastric cancers have more extensive lymph node metastases. Malignant cells frequently replace most of these nodes and invade the perinodal fatty tissue[77] We believe that this high-risk group should be treated in the same way as those with advanced cancers, by means of complete lymph node dissection (R_2 or R_3) including the perinodal fatty tissue, using the no-touch isolation technique[85] or circulatory blockade to prevent haematogenous metastasis[47,80]. There are some who would argue in favour of postoperative adjuvant chemotherapy for this high-risk group[7,11,47,66,80,86].

Endoscopic surgery for early gastric cancer

Endoscopic surgery for the treatment of gastric cancer was first used in patients with severe co-existing medical disorders in whom resection was considered to be contraindicated or in those refusing surgery. Recently, some clinicians consider that for selected patients with early gastric cancer this procedure might be justified to achieve radical cure. The problem with endoscopic surgery is that staging must be very accurate because metastatic lymph nodes cannot be treated.

Minute lesions may be successfully treated, but large ones are difficult to cure completely by endoscopic therapy and require repeated treatments. Evaluation of the efficacy of treatment requires long-term follow-up with repeated biopsies. In addition, postoperative ulceration may enhance invasion to the deep layers by residual cancer cells. Radical endoscopic therapy is indicated only for patients who are thought to have no lymph node metastasis Patients who are least likely to have lymph node involvement are those with elevated type I or IIa mucosal cancers of less than 2 cm diameter and those with IIc mucosal cancers less than 1 cm in diameter without an ulcer[12,73,87–89].

The following endoscopic methods are being used: (1) laser surgery[50,87,89,90]; (2) high frequency electric current polypectomy or strip biopsy known as mucosectomy[91–94], (3) microwaves[95,96] and (4) local injections[97,98]. Of these, laser surgery is most widely used as it is easier than the other methods but requires expensive equipment. Strip biopsy or mucosectomy introduced by Tada *et al.*[92,99] was developed to obtain biopsies as large as 2–3 cm in diameter. The technique involves injections of physiological saline into the submucosa under the lesion to create a small swelling which is resected using a high frequency snare. This procedure permits resection of a block of tissue 1–2 cm in diameter. A further advantage is that histological examination of the resected specimen allows confirmation of the integrity of the resection and determination of vascular invasion as well as histological type of malignancy.

In 1986, Kasugai *et al.*[100] accumulated data on the endoscopic treatment of early gastric cancer from 71 hospitals; 1653 cases were studied and the proportion with no evidence of total recurrence for more than a year after treatment was 85 per cent for laser therapy and 99 per cent for high frequency therapy

Endoscopic surgery is a valuable technique for elderly, poor risk patients and those refusing surgery, but must only be undertaken using strict criteria and careful follow-up if the aim of therapy is radical cure. This is because early gastric cancer can usually be cured by surgical treatment. For both endoscopic and conventional surgical excision, an accurate descriptive and histological diagnosis is essential to predict the likelihood of lymph node involvement and local infiltration which determines optimum therapy.

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Adrenal insufficiency in the cancer patient: implications for the surgeon

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Aspects of acute and chronic adrenal insufficiency of interest to surgeons who treat cancer patients are reviewed. Clinical features and the management of both primary and secondary types are considered with reference to classification, aetiology, diagnosis and treatment. Specifically considered are the management of patients with Addison's disease and metastases. Prompt recognition and treatment of adrenal insufficiency can avert potentially life-threatening situations.

Keywords: Adrenal, Addison's disease, metastases

Adrenal insufficiency may go unrecognized in the cancer patient because features such as nausea, vomiting, anorexia and orthostatic hypotension are not specific and may be mistakenly attributed to advancing malignancy or side effects of therapy. This report reviews those aspects of acute and chronic adrenal insufficiency of pertinence to any surgeon who treats cancer patients, comparing and contrasting clinical features and management of both primary and secondary types.

Classification

In primary adrenal insufficiency (Addison's disease) all three functional zones of the adrenal cortex are impaired causing varying degrees of glucocorticoid, mineralocorticoid and adrenal androgen deficiencies[1]. Secondary adrenal insufficiency is characterized by pure glucocorticoid deficiency due to decreased adrenocorticotropic hormone (ACTH) or corticotropin releasing factor (CRF) reserve with subsequent atrophy of the zona fasciculata. Mineralocorticoid deficiency does not occur if primary non-pituitary stimuli for aldosterone secretion, such as serum potassium and the renin-angiotensin system, remain intact.

Aetiology

Autoimmune or granulomatous diseases are the leading causes of Addison's disease in the general population[1]. In the cancer patient, primary adrenal insufficiency may develop from replacement of both glands by metastases or infiltration with lymphoma[2–8], removal of both glands, or haemorrhagic necrosis in association with anticoagulation or sepsis as seen in the Waterhouse–Friderichsen syndrome[9]. Impaired adrenal steroidogenesis occurs in patients taking aminoglutethimide[10], ketoconazole[11], mitotane (*o'p*-DDD)[1], or the investigational agent suramin[12].

Although approximately 22 per cent of patients dying from adenocarcinoma have adrenal metastases, most often from lung, breast, colon or kidney primaries, only 1–5 per cent of patients with Addison's disease occur on this basis[5]. Over 90 per cent of functioning adrenal tissue must be replaced or destroyed for homonal insufficiency to occur[5,8,9]. However, the occurrence of adrenal insufficiency may not be an uncommon consequence of metastasis, as both retrospective[4] and prospective[13] series have demonstrated that up to a third of patients with metastatic disease and bilateral adrenal gland enlargement as assessed by computed tomographic scan will develop biochemical and clinical adrenal insufficiency. Their symptoms including nausea, anorexia and orthostatic hypotension were promptly relieved by replacement therapy[4,13] Rarely, metastatic replacement will cause symptomatic primary adrenal insufficiency as the first manifestation of an occult malignancy[14].

Metastasis to the pituitary or hypothalamus is found at autopsy in up to 5 per cent of patients with cancer[15] but associated secondary adrenal insufficiency is rare. Hypoadrenalism was documented in 21 per cent of patients with nasopharyngeal malignancies treated by radiation[16]. Suppression of CRF or ACTH production is commonly associated with pharmacological corticosteroid therapy or functioning adrenal tumours[9] Acute insufficiency may follow removal of a steroid-producing tumour because of chronic suppression of the contralateral gland and may occur despite normal preoperative basal cortisol levels[17]. Further testing will confirm inadequate cortisol production by the remaining gland.

Pharmacological corticosteroid therapy is used in a variety of cancer treatment programmes and is the most common cause of secondary adrenal insufficiency in cancer patients. Hypoadrenalism has been reported after MOPP (methotrexate, Oncovin (vincristine), prednisone, procarbazine) chemotherapy for lymphomas[8]. Many other repetitive chemotherapy regimens include corticosteroids or use them adjunctively as antiemetic or antipyretic agents. Patients with brain or spinal cord metastases are commonly treated with pharmacological steroid doses to reduce swelling Secondary insufficiency may follow inadvertent omission, too rapid tapering, or inadequate dosage during stress.

Clinical features

Symptoms of adrenal insufficiency are often subtle and not specific. Presenting features typically include nausea and hypotension, and vomiting, diarrhoea, vague abdominal or flank pain, and confusion may occur[19]. Because these are also symptoms of progressive or disseminated disease, a high index of suspicion is required. Mild fever, arthralgias, and weakness or fatigue often precede more serious complaints. Intravascular fluid deficit may develop, leading to tachycardia, progressive hypotension and shock, a constellation termed 'adrenal crisis'.

Hyperpigmentation of elbows, knees, lips or palmar creases are signs of long-standing primary insufficiency[19]. In at least half of the patients, hyponatraemia or hyperkalaemia may be present, common biochemical abnormalities also include moderately elevated urea nitrogen levels and mild acidosis.

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Hypoglycaemia due to impaired gluconeogenesis and hypercalcaemia related to renal excretion, bone resorption and haemoconcentration are occasional features[1]. While eosinophilia or lymphocytosis may be noted, their absence does not rule out adrenal insufficiency[19]. Clinical features of secondary adrenal insufficiency are more subtle, and prominent electrolyte abnormalities of Addison's disease such as hyperkalaemia are lacking[1]. Hyponatraemia usually reflects decreased free-water clearance with antidiuretic hormone (ADH) and ADH-independent intrarenal factors implicated in its pathogenesis Hyperpigmentation is not seen in secondary adrenal insufficiency since the melanocyte-stimulating activity of ACTH or β-lipotropin is absent.

Diagnosis

Elevated basal plasma ACTH levels and low unresponsive serum cortisol and aldosterone levels confirm the diagnosis of primary adrenal insufficiency. Testing is accomplished by an ACTH stimulating test as follows: after basal sampling, 0·25 mg of the synthetic ACTH preparation tetracosactrin is given intravenously or intramuscularly, and plasma cortisol and aldosterone levels are drawn at 30 and 60 min. The difference between basal and stimulated cortisol values should be at least 6–7 μg/dl (165–195 nmol/l) with a maximum cortisol value of 18–20 μg/dl or greater (>550 nmol/l)[1,17,20]. If there is insufficient time for testing, serum cortisol and ACTH levels should be sampled before institution of steroid replacement therapy. In stress situations, a cortisol level of 10 μg/dl (275 nmol/l) or less with a concurrent ACTH level greater than 200 pg/ml reliably establishes the diagnosis.

In suspected secondary adrenal insufficiency, evaluating hypothalamic and pituitary reserve by insulin-induced hypoglycaemia or metyrapone testing is cumbersome and uncomfortable. Because plasma cortisol response to ACTH correlates best with adrenocortical response to clinical stress, the ACTH stimulation test is preferred[21,22].

It is difficult to define precisely the smallest dose of corticosteroid or the shortest time of administration that causes hypothalamic–pituitary axis (HPA) suppression. Any patient who has received the equivalent of 20–30 mg prednisone daily may have HPA suppression of potential clinical significance[23,24]. Biochemically demonstrable HPA suppression may persist for a year or more after treatment[24]. Since any dose of steroid in excess of basal replacement doses can theoretically impair HPA response, all previously treated patients exposed to the stress of trauma, operation or sepsis should be considered as at risk.

Treatment

Acute adrenal insufficiency is potentially lethal. Treatment of suspected adrenal crisis is initiated after sampling serum cortisol and ACTH levels. Unexplained hypotension refractory to standard therapy is treated with hydrocortisone 100 mg intravenously every 6–8 h in addition to volume expansion with normal saline and glucose[19,20] In primary adrenal insufficiency, hydrocortisone has adequate mineralocorticoid activity at this dosage. Parenteral therapy is continued for at least 24 h after recovery and maintenance glucocorticoid doses are initiated or resumed within 72 h. In Addison's disease with hyperkalaemia, maintenance mineralocorticoid therapy is required Normal production of cortisol is 15–20 mg/day and most hypoadrenal patients require 30–40 mg/day. This is customarily given orally as cortisone acetate 25 mg every morning and 12·5 mg in the evening[1] or the equivalent daily dose of hydrocortisone (30 mg), prednisone (5–7·5 mg) or dexamethasone (0·5–1·0 mg). Addison's disease also requires fludrocortisone acetate (0·1–0·2 mg) daily or every other day to control hyperkalaemia, renal sodium wasting and orthostasis[1]. The dose of cortisone should be tripled whenever fever occurs and given parenterally (100 mg) during periods of illness. Patients are strongly advised to wear a 'Medi-alert' bracelet or pendant to advise others of their chronic needs should they become incapacititated.

Serious illness, trauma or general anaesthesia requires intravenous infusion of 300 mg cortisol hemisuccinate daily in patients on chronic therapy. Should the event occur during planned steroid withdrawal, the same policy is followed with resumption of tapering at doses which are 10–15 per cent higher than previously given[24]. Minor physiological stress within a year of discontinuing therapy is managed with 50–100 mg oral hydrocortisone daily, tapering over 5–10 days. Major stress requires 100–300 mg cortisol hemisuccinate intravenously on a daily basis, withdrawing over 2 weeks[23,24].

Surgeons should be familiar with clinical settings in which occult or overt insufficiency may occur in cancer patients. Prompt recognition and treatment will avert a potentially life-threatening situation and enhance the quality of life in those suffering the incapacitating consequences of hypoadrenalism.

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Changes in cardiovascular homeostasis after injury are mediated by tissue damage and not haemorrhage

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During treatment of the injured patient it is assumed that the cardiovascular responses follow recognized physiological principles. Studies in humans have shown that injury causes a profound suppression of arterial baroreflex function which alters the normal relationship between heart rate and blood pressure and casts doubt on this assumption. To investigate the mechanism of baroreflex suppression, we have studied the effects of the two major components of injury, blood loss and tissue damage, on baroreflex function in healthy volunteers. Baroreflex function was assessed using suction stimulation of the carotid sinus. The loss of 500 ml blood had no effect on baroreflex sensitivity. A human laboratory model of tissue injury reduced the ability of the baroreflex to compensate for a rise in blood pressure ($P < 0.05$, *Wilcoxon signed rank test). We conclude that tissue damage, rather than hypovolaemia, appears to mediate the effect of injury on baroreflex function in the injured. Blockade of neural signals from damaged tissue may have a role in the treatment of injury.*

Keywords: Baroreflex, haemorrhage, trauma

After injury or haemorrhage, resuscitation is directed at maintaining or restoring tissue perfusion. The speed and accuracy of this treatment is a major factor in preventing complications such as multiple organ failure by the avoidance of hypoxia, acidosis and the subsequent activation of cascades of inflammatory mediators. Intravenous fluids and other treatments interact with innate homeostatic mechanisms, in particular those of the cardiovascular system. The mechanism of prime importance in this respect is the arterial baroreflex, which maintains blood pressure through reflex autonomic adjustments of heart rate and peripheral resistance.

After tissue injury a number of changes in physiological systems occur remote from the injured part, constituting a systemic response to injury. Endocrine and metabolic responses to injury are well recognized, but we have recently shown that injury is also associated with a marked suppression of baroreflex function in animals and in humans[1–3] This suppression is rapid in onset, profound, and of at least 2 weeks duration even after moderately severe injury. During this time changes in blood pressure are no longer met by the usual compensatory changes in heart rate[3]. These findings implied that injury results in marked derangement of cardiovascular homeostasis.

It is not known how these changes in homeostasis are mediated. Investigations should clarify their significance and reveal possible ways of modifying them. Haemorrhage[4] and tissue damage[5] are the two classical components of injury which stimulate systemic responses. Differences have been recorded in the cardiovascular responses to isolated haemorrhage, to haemorrhage with tissue damage, and to injury alone in rats and in humans[1,6,7]. These differences may contribute to the observation that survival is more likely after haemorrhage than after injury with a similar volume of blood loss[8,9]. To identify the mechanisms responsible for changes in cardiovascular homeostasis after injury we have examined the effects of these factors on the baroreflex in healthy human subjects and drawn comparisons with responses in injured patients.

Patients and methods

The baroreflex exists to maintain blood pressure and an inverse relationship exists between blood pressure and heart rate. When the inverse of heart rate, known as heart period (or the R–R interval of the electrocardiograph) is taken, a linear relationship is described. The gradient of the relationship indicates the magnitude of reflex change in heart period that will be brought about, by the baroreflex, to compensate for any given primary change in blood pressure This gradient is therefore an index of baroreflex sensitivity[10–12].

Baroreflex sensitivity is studied by changing the blood pressure and recording subsequent changes in heart period[11,12]. Causing actual change in blood pressure might be hazardous to the injured or hypovolaemic patient, so an indirect method, the neck chamber method, was used[10,12] Carotid baroreceptors respond to the transmural pressure gradient. By enclosing the neck in a pressure chamber, the extramural pressure can be altered, thus stimulating the baroreceptors without changing blood pressure significantly. Neck suction mimics a rise in blood pressure in a well tolerated and highly quantifiable fashion[13]

We assessed baroreflex sensitivity by applying neck suction at multiple presures between 0 and −50 mmHg for brief periods (two heart periods, *Figure 1*), at 1 min intervals, over a 30 min test period, as previously reported[3]. The change in heart period caused was plotted against applied suction pressure and the gradient of the relationship was calculated by the method of least squares line of best fit and taken as an index of baroreflex sensitivity (*Figure 2*) Testing was performed in the supine position and blood pressure was recorded before testing using a Dinamap 845 semi-automatic monitor (Critikon, Tampa, Florida, USA).

Four groups of subjects were studied. Twenty-two healthy colleagues (15 men, seven women; age range 18–53 years, median 27 years) served as a control group.

Twelve of the control group underwent baroreflex testing before, and within 30 min of completing, a venesection of 500 ml performed by the staff of the Blood Transfusion Service. The venesection was performed within 30 min of the initial test of baroreflex sensitivity, and blood pressure was recorded before each neck suction test.

The principal difference between injury and haemorrhage is the presence in the former of damaged tissue Tissue injury is believed to

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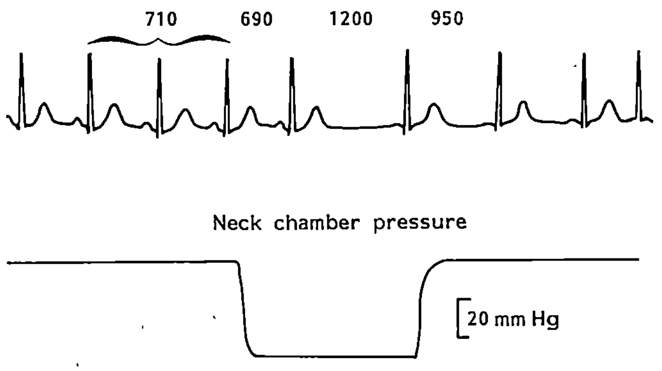

Figure 1 *Trace of single application of neck suction showing rapidity of cardiac response on the electrocardiograph. The response is quantified by subtracting control heart period (bracketed average of two heart periods preceding suction onset) from the longest of three heart periods following*

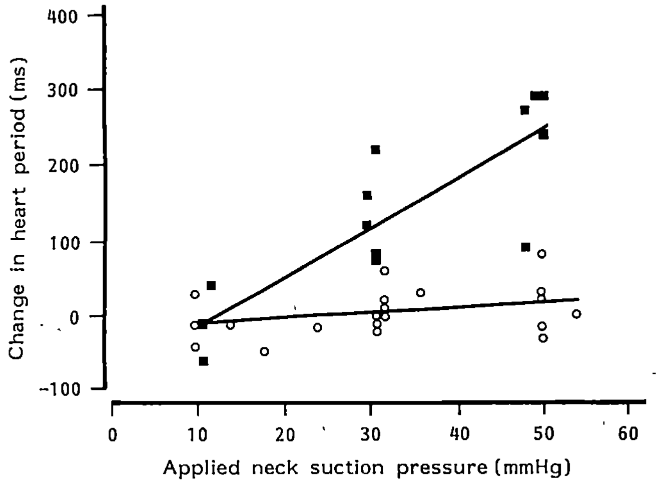

Figure 2 *Plots of change in heart period in response to neck suction at two times in an injured patient.* ○, *2 h after fracture of the right tibia and fibula,* ■, *10 days later. Neck suction is a quantitative mimic of change in blood pressure and the gradient of the relationship therefore indicates baroreflex sensitivity. Injury causes the gradient of the relationship to be reduced, baroreflex suppression has occurred and the relationship between heart period and blood pressure has been lost. Recovery is evident 10 days later*

result in the stimulation of local nociceptors which signal their activation through afferent neural pathways[1,6,8]. A second subgroup of ten subjects underwent neck suction testing of baroreflex sensitivity before and after the inflation of a thigh blood pressure cuff[6]. The cuff was inflated to 20 mmHg above thigh systolic pressure for 10 min to provide nociceptive stimulation. Then, with the thigh cuff still inflated, at least three neck suction measurements were made at a pressure previously shown to cause considerable slowing of the heart.

The final group comprised 21 injured patients who were otherwise healthy and of similar age and sex to the control group (19 men, two women; age range 16–52, median 27 years). Eighteen patients had long bone fractures of the lower limb and the other three patients had injuries of similar severity[3,14]. The patients were treated independently and routinely by appropriate staff. Baroreflex testing was performed at four times after injury. Nine patients were studied between 2 and 4 h (median 3 h) of injury, one had received intravenous fluids, seven had received opiate analgesia, and one nitrous oxide–oxygen mixture. The opiates had been given at least 30 min before testing (range 0·5–2 h, median 1 h) Eighteen patients were studied 2–4 days (median 3 days) after injury, of whom 15 had undergone surgery. This had been carried out at least 36 h before testing (range 36–90 h, median 66 h). Fifteen patients were studied for 7–17 days (median 15 days) after injury. Seven patients were studied after recovery (7 weeks to 10 months, median 5 months, after injury).

Baroreflex sensitivity was not normally distributed in the control group so statistical analysis of differences between baroreflex sensitivities in the different groups was performed using Wilcoxon's rank sum and signed rank tests as appropriate Differences in baroreflex sensitivity obtained from the same person at different points in time were assessed using Satterthwaite's t' test[15].

Results

Effect of injury on baroreflex sensitivity

In comparison with controls, injury caused marked suppression of baroreflex sensitivity (*Table 1*). This suppression was evident even within 4 h of injury ($P<0·05$, Wilcoxon rank sum test) and was uniform and intense by 3 days after injury ($P<0·001$, same test). Recovery of baroreflex sensitivity was seen thereafter. Of 13 patients studied 3 days and then 15 days after injury, recovery was seen in each case ($P<0·005$, Wilcoxon signed rank test). Four of these individual increases in baroreflex sensitivity were significant ($P<0·05$, Satterthwaite's t' test, see *Figure 2*) while two more just failed to reach this level ($P<0·1$). In comparison with controls, baroreflex sensitivity remained suppressed even 2 weeks after injury ($P<0·05$, Wilcoxon rank sum test). By the time the patients had recovered clinically, their baroreflex sensitivity was no longer different from that of controls. The effect of injury on baroreflex sensitivity was fully reported in our previous paper[3].

Effect of haemorrhage on baroreflex sensitivity

Control baroreflex sensitivity in the 12 subjects who underwent baroreflex testing before and after 500 ml venesection was no different from that recorded in the other control subjects (Wilcoxon rank sum test). Haemorrhage caused no change in heart rate, which was (group mean (standard error)) 65·3(3·2) beats/min before blood loss, and 66·5(3·6) beats/min afterwards (difference not significant, Wilcoxon signed rank test), but systolic blood pressure fell from 125·9(4·1) to 115·2(6·7) mmHg ($P<0·02$, Wilcoxon signed rank test). Overall, 500 ml haemorrhage had no effect on baroreflex sensitivity. Median baroreflex sensitivity was 3·3 ms/mmHg (range −0·1 to 18·5 ms/mmHg) before haemorrhage and 3·5 ms/mmHg (range 0·4–14·7 ms/mmHg) afterwards (difference not significant, Wilcoxon signed rank test). Seven subjects showed greater baroreflex sensitivity after haemorrhage, while five showed a lesser response to neck suction. Two of the individual increases in baroreflex sensitivity and one of the decreases were significant when assessed by Satterthwaite's t' test.

Effect of an inflated thigh cuff on baroreflex sensitivity

Inflation of the cuff caused only a transient ache and all subjects tolerated 15 min of cuff inflation. Baseline heart rate was 60·7 (45·2–75·4) beats/min and 62·7 (46·7–82·5) beats/min once the cuff was inflated (difference not significant, Wilcoxon signed rank test). The median neck suction pressure used to test baroreflex sensitivity with the cuff inflated was 46·5 mmHg (range 40–50 mmHg). The heart slowing produced by neck suction was reduced when the thigh cuff was inflated in seven of the ten tests, a significant difference overall ($P<0·05$, Wilcoxon signed rank test, *Figure 3*). Reflex slowing of the heart fell from a median of 237 ms (range 43–540) to 122 ms (range 27–630) once the cuff was inflated.

Table 1 *Baroreflex sensitivity in control group and at different times after injury*

Group	Range (ms/mmHg)	Median (ms/mmHg)
Controls	0·1 to 15·5	3·7
Injured		
3 h	−0·6 to 6·8	1·1
Day 3	−0·1 to 2·8	1·4
Day 15	−0·1 to 6·5	2·6
Recovered	1·2 to 8·3	2·1

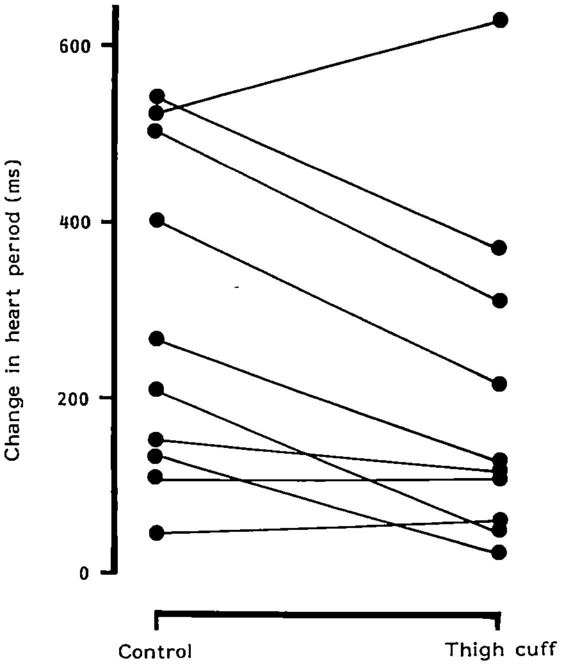

Figure 3 *The effect of nociceptive stimulation from a thigh cuff (a model of tissue damage) on the baroreflex. Overall* (n = *10*) *the ability of the heart to compensate for a rise in blood pressure was reduced* ($P<0.05$, *Wilcoxon signed rank test*)

Discussion

Baroreflex suppression occurs after injury in man. The suppression is apparent within 4 h of injury and persists for at least 2 weeks. During this time, increases in blood pressure are not met by the normal compensatory reflex slowing of the heart. The results of these specific studies of human baroreflex function were considered in detail previously[3] and are supported by earlier non-specific human and animal data[1,2]. There can be little doubt that a genuine effect has been observed, but its causation is unclear. Apart from hypovolaemia and tissue damage, consideration must be given to the influence of opiates, anaesthesia, surgical intervention and the mental stress of injury on the baroreflex and the cardiovascular system.

Venesection of 500 ml had no consistent effect on baroreflex sensitivity, it did not reproduce the effects of injury. While this degree of haemorrhage is minor, it is probably similar to the degree of hypovolaemia present in the nine patients studied within 4 h of injury. It can be inferred that the baroreflex suppression that occurs after injury is not due to circulatory fluid loss.

These results also suggest that the response of the baroreflex to haemorrhage is different from the response to injury. Rats subjected to a haemorrhage of 20 per cent of circulating volume show an increase in baroreflex sensitivity[6], the opposite response to that found by the same group in rats subjected to experimental injury[1]. Furthermore, the Valsalva ratio is increased after 500 ml venesection in man, yet reduced after accidental limb fracture[2,6]. The present study failed to demonstrate an increase in baroreflex sensitivity after haemorrhage, but the blood volume removed was proportionally half that required to do so in the rat. The increase in cardiovascular reflex activity suggested by the Valsalva studies[6] may have been due to the test which itself sequesters a further volume of blood within the venous side of the circulation. Thus, the available evidence suggests that hypovolaemia, in the absence of tissue damage, probably brings about an opposite effect to tissue damage on the function of the baroreflex

The inflation of a thigh cuff to suprasystolic pressure for 10 min was used to stimulate nociceptors, and this reproduced some of the effects of injury. Heart slowing in response to a perceived rise in blood pressure was reduced but, with measurements at only one pressure, it was impossible to state whether the regression line had shifted sideways (indicating a change in the set point of the reflex) or whether the gradient had been reduced (indicating a fall in baroreflex sensitivity), as occurred in the injured patients. Supporting evidence suggests that baroreflex sensitivity had fallen Firstly, there was no change in baseline heart rate to suggest that a parallel shift of the regression line accounted for the diminished response to neck suction. Secondly, it has been shown conclusively that baroreflex suppression in the injured rat is brought about by neural signals which originate in the injured limb[1]. Most interestingly, the response to the damaged tissue in the rat can be prevented by surgical sectioning or pharmacological blockade of the afferent neural fibres from the injured limb. The data from this and an earlier human study[6] make it likely that stimulation of these receptors in the damaged tissues brings about baroreflex suppression in humans as well as in the injured rat.

The influences of analgesia and anaesthesia are pertinent. Besides the effects of nerve section reported above[1], Overman and Wang found that spinal anaesthesia prevented the cardiovascular responses to their animal model of injury[8]. In humans, preoperative epidural analgesia[16] or high-dose fentanyl analgesia[17] substantially modify the hormonal response to surgical trauma. Preoperative fluid loading does not have the same effects[18]. In the rat the baroreflex suppression of injury can be reversed by naloxone[19], while in dogs the function of the baroreflex in haemorrhage is unaffected by morphine[20] These further differences in the responses to injury and haemorrhage also indicate the possible role of the endogenous opioid system. Certain endogenous opioids can suppress baroreflex sensitivity in normal humans[21] No conclusions could be drawn from the injured patients in this study, but it is reasonable to suggest that the earlier analgesia is given the greater effect it might have in preventing systemic responses. It may be that these responses are irretrievably activated by the time of arrival at hospital.

Anaesthesia suppresses baroreflex activity but recovery is complete within minutes of the end of the anaesthesia[22]. Only three of the patients had undergone a procedure more traumatic than insertion of a skeletal traction pin, so operative trauma would have been minor and the achievement of bony stability must have reduced the subsequent nociceptive stimulation. The improvement in survival after prompt, definitive orthopaedic surgery[23] confirms the belief that reduction of wound size and the systemic response are beneficial[24].

The mental stress of injury is significant. It can, on its own, activate the defence response (fight or flight reaction) in animals[25,26], and psychological factors have a significant effect in the endocrine response to moderate injury[27]. There is no satisfactory quantitative method of inflicting mental stress experimentally, mental arithmetic being the only accepted technique[28]! Mental stress causes an increase in heart rate resulting in a parallel displacement of the blood pressure–heart period relationship, but baroreflex sensitivity is not changed[29].

It is not clear why the effect of injury on cardiovascular homeostatic reflex activity should be the opposite to the effect of haemorrhage. Since the time of John Hunter, it has been considered that an animal's responses to injury are beneficial to survival in the face of predation[24]. The changes in cardiovascular homeostasis after injury fit this pattern, although the necessary vasoconstriction may result in reduced longer term survival as a result of cellular hypoxia[8]. When haemorrhage and tissue damage coexist, the homeostatic response is similar to that seen after injury[1] Humans seldom need to fight their injuring force, and their systemic responses may be detrimental rather than beneficial. Certainly, some change in our understanding and management of the trauma victim is necessary, because as many as 20 per cent of the deaths from injury are caused by the uncontrolled physiological derangements of the multiple organ failure syndrome[30]. Current early treatment of injury focuses almost exclusively on restoration of circulating volume. Accurate and rapid fluid therapy is essential, but the evidence now suggests that neural signals from the injured tissues play an important part in the mediation of the cardiovascular responses to injury. Modulation of these responses may be possible. Research into the endogenous opioid system shows promise[31] and the effect of very early epidural anaesthesia on the systemic responses to major lower limb and pelvic injury, under appropriately controlled conditions, could be usefully investigated. A new therapeutic avenue for the prevention of systemic complications of major accidental and surgical trauma might be identified.

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Adrenergic control of the internal anal sphincter is abnormal in patients with idiopathic faecal incontinence

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There is histological and functional evidence that the internal anal sphincter is abnormal in patients with idiopathic faecal incontinence. The in vitro *responsiveness of the internal anal sphincter to noradrenaline (an important sympathetic neurotransmitter) and electrical field stimulation (known to stimulate the intrinsic innervation) has been studied. Muscle strips from eight patients with incontinence undergoing postanal repair and five controls undergoing resection for low rectal carcinoma were studied. The contraction–response curves for noradrenaline were significantly different, and the EC_{50}, the concentration required to produce 50 per cent of maximum contraction, was higher in incontinent patients* ($P<0{\cdot}001$). *Electrical field stimulation produced initial contractions in four of the control group which were blocked by phentolamine. This contraction was not present in the incontinent patients* ($P<0{\cdot}01$). *These results indicate an abnormality in the adrenergic innervation of the internal anal sphincter in patients with idiopathic faecal incontinence.*

Keywords: Innervation, internal anal sphincter, electrical field stimulation, noradrenaline

In idiopathic faecal incontinence (IFI) there is denervation of the striated pelvic floor muscles[1–7]. There is increasing evidence that the internal anal sphincter is also abnormal in these patients. Manometric studies have shown that in approximately two-thirds of patients with faecal incontinence the maximum resting anal pressure, which is mainly produced by internal sphincter activity[8–10], is abnormally low[2]. Ultrastructural studies have demonstrated fibrosis and atrophy of the internal anal sphincter in patients with neurogenic incontinence[11,12]. A hypothesis is that there may be damage to the innervation of the internal anal sphincter in idiopathic faecal incontinence. This was tested by analysing the *in vitro* response of the internal anal sphincter from patients with IFI to noradrenaline, an important sympathetic neurotransmitter in the internal anal sphincter, and to electrical field stimulation (EFS), which is known to stimulate non-adrenergic, non-cholinergic intrinsic nerves in the internal anal sphincter, as well as the intramural sympathetic nerves[13].

Patients and methods

Patients

Eight patients undergoing postanal repair for incontinence to solid stool were studied. There were seven women and one man, mean (range) age of 57 (39–79) years. Five of these patients had previously had forceps deliveries and the other two women had had two and four vaginal deliveries.

Controls

Two women and three men, mean (range) age 57 (44–74) years were studied as controls. These were patients undergoing abdominoperineal resection for low rectal carcinoma. None of the controls had a history of faecal incontinence.

The study was approved by the City and Hackney District Ethical Committee of St. Bartholomew's Hospital.

Methods

Anorectal physiology. Anorectal physiology was performed before operation in all incontinent subjects. None of the control patients was incontinent and they did not undergo anorectal physiology studies. Maximum resting anal pressure and maximum voluntary contraction pressures were measured using a closed water-filled system with a 4 mm diameter microballoon[2]. Pudendal nerve terminal motor latencies and single fibre electromyography of the external anal sphincter were performed using previously described methods[1,3].

Tissues studied. During the intersphincteric dissection of postanal repair a 10 mm long by 3 mm wide circumferential (transverse) strip of the internal anal sphincter was taken and placed into Krebs' solution. The control tissue was taken from the resected abdominoperineal specimen, removing the equivalent most distal strip of the posterior internal anal sphincter.

In vitro *experiments.* The tissue removed was dissected into 2–4 strips and the presence of smooth muscle was confirmed using a dissecting microscope. The muscle strips were suspended in 3 or 5 ml organ baths containing modified Krebs' solution containing 0·1 per cent bovine serum albumin and the bacterial inhibitor bacitracin (1500 units l^{-1}) at 37°C and perfused with 95 per cent O_2 and 5 per cent CO_2. Contraction and relaxation responses were recorded via transducers on a Grass (Grass Instruments Co., Quincy, Massachusetts, USA) polygraph under auxotonic conditions. Each experiment was performed on 2–4 strips from each patient. Noradrenaline was added to the organ baths in increasing concentrations (10^{-8}–10^{-4} M) until the maximum contraction had been obtained. After each addition of noradrenaline the strips were washed with Krebs' solution. The concentration of noradrenaline required to achieve maximum contraction was determined for each muscle strip. The mean concentration of noradrenaline required to achieve different proportions of maximum contraction for the two groups was then calculated. From the responses obtained to increasing concentrations of noradrenaline, a concentration–response curve was constructed and the concentration required to produce 50 per cent of the maximum contraction, the EC_{50}, was calculated for each group. EFS was produced by two platinum electrodes immersed in the organ bath. Optimum relaxant responses were obtained using stimulation of 150 V and pulse duration of 0·5 ms. Responses to a range of stimuli (1–32 Hz) were recorded.

Results

Anorectal physiology

The results of the anorectal physiology are compared with normal values obtained from over 200 controls studied in our

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laboratory. The mean (range) maximum resting anal pressure was 28 (5–60) cmH$_2$O. All patients were therefore at the lower limit or below the normal range (40–100 cmH$_2$O). The pudendal nerve terminal motor latency was prolonged in all patients (mean (range) 2·6 (2·4–3·0) ms, normal $\leqslant$2·2 ms (reference 3)). The single fibre density of the external anal sphincter was raised (mean (range) 2·27 (1·8–2·7) ms, normal $\leqslant$1·7 ms (reference 1)) in all patients. These results indicate that all the incontinent patients studied had evidence of denervation of the striated pelvic floor musculature.

In vitro *responses*

Noradrenaline. The isolated muscle strips from both the incontinent patients and controls contracted to noradrenaline (*Figure 1*) and the magnitude of contraction increased with increasing concentrations of noradrenaline. The active contraction by all muscle strips indicated the presence of viable muscle. The mean EC$_{50}$ was significantly higher ($P<0{\cdot}001$, unpaired t test) in the incontinent group.

From the concentration–response curves (*Figure 2*), it can be seen that for each response (proportion of maximum contraction), the concentration of noradrenaline required to produce that given response was higher in the incontinent group. Because of the inevitable variation in the mass of the individual muscle strips, the absolute value of the contraction of each strip has not been compared.

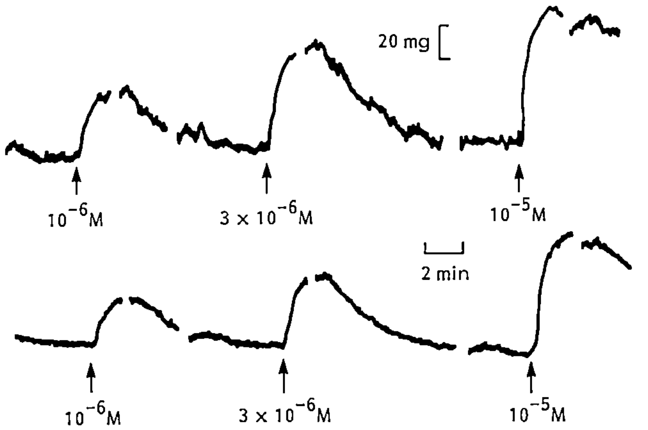

Figure 1 *Polygraph recordings of two muscle strips from an incontinent patient showing larger contractions to increasing concentrations of noradrenaline (10^{-6}–10^{-4} M). Noradrenaline was applied (arrows) at the concentrations indicated*

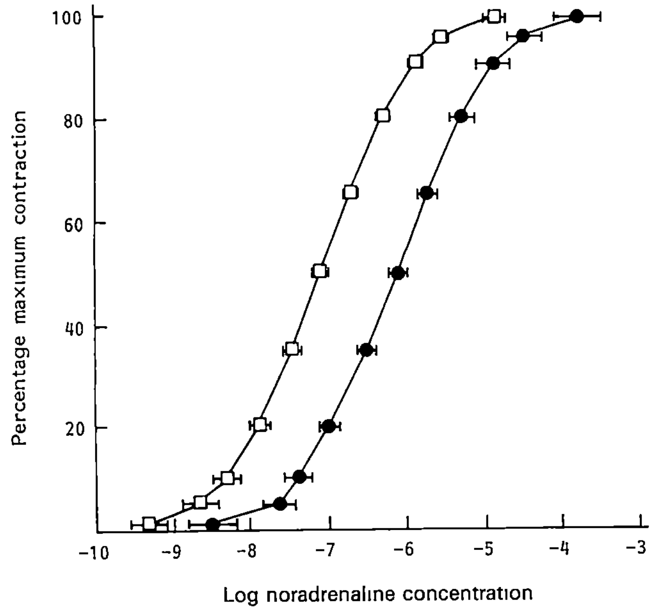

Figure 2 *Concentration–response curves for noradrenaline in five controls (□) and eight incontinent patients (●) with standard errors*

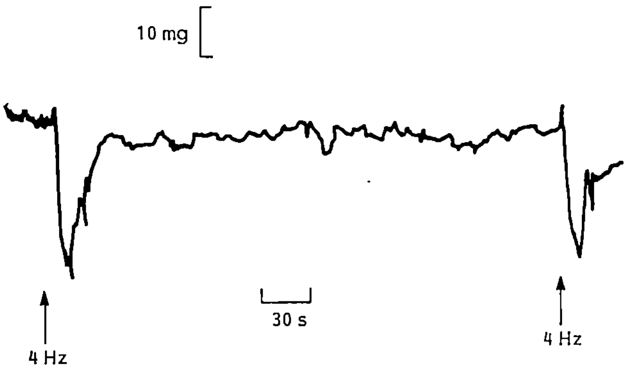

Figure 3 *Response to electrical field stimulation in a control demonstrating an initial small contraction followed by a larger relaxation*

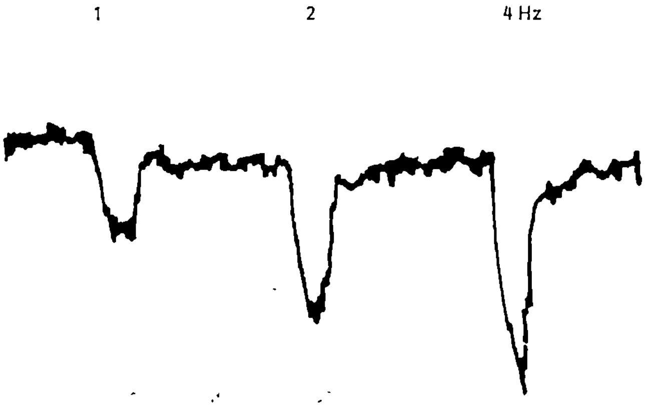

Figure 4 *Response to electrical field stimulation in the same muscle strip as seen in* Figure 3 *after the addition of phentolamine*

Electrical field stimulation. EFS produced relaxations in all strips, but in four out of the five controls there was an initial small contraction (*Figure 3*). This small contraction was blocked by the addition of the α-blocker phentolamine (*Figure 4*). There was no similar contraction in the incontinent group. This difference was significant ($P<0{\cdot}01$, Kolmogorov–Smirnov non-parametric test).

Discussion

Our results show that the internal anal sphincter from patients with idiopathic faecal incontinence was less sensitive to noradrenaline than that from control patients.

The internal anal sphincter is known to receive a dense extrinsic sympathetic innervation[14] but its role in humans remains controversial. There is evidence suggesting that it is responsible for internal anal sphincter contraction[15–18] or relaxation[19,20]. These differences may relate to different stimulation parameters employed in each study. Evidence from animal studies indicates that the sympathetic innervation of the internal anal sphincter is excitatory[21–24]. This study demonstrates a decreased sensitivity to noradrenaline and may, therefore, reflect a diminished sensitivity of the sphincter to one of its major innervators.

In this study the sensitivity to noradrenaline, rather than the absolute value of the maximum contraction, has been measured. Differences between the patients and controls in the amount of fibrous tissue in the sphincter would therefore not account for these results.

The finding in several control patients of an initial small contraction in response to electrical field stimulation, blocked by the α-blocker phentolamine, suggests that this is due to an α-adrenergic mediated mechanism. These initial contractions to EFS have been reported previously[25], but this is the first demonstration that α-adrenergic receptors are responsible.

These *in vitro* studies demonstrate abnormal sphincter responsiveness to neural control in idiopathic faecal incontinence. This complements recent *in vivo* studies which have demonstrated abnormalities of sphincter behaviour, and therefore possibly innervation, in this condition. In one study performed at rest, episodes of spontaneous relaxation occurred less frequently in patients with IFI than in controls[26] In an ambulatory study episodes of anal relaxation were more frequent and prolonged in patients with IFI compared with controls[27].

The extrinsic sympathetic supply to the internal anal sphincter could be damaged by several mechanisms. Injury may occur simultaneously with the damage to striated muscles as part of the stretching of the pelvic floor. Alternatively there may be a primary intrinsic degeneration of the muscle and its receptors. Lack of support from a damaged external anal sphincter may also be a factor[11]. The diminished *in vitro* sensitivity of the internal anal sphincter to sympathetic stimulation may be of primary pathogenic importance in idiopathic faecal incontinence. Further pharmacological studies are required to define this abnormality better.

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Adjuvant chemotherapy with 5-fluorouracil, vincristine and CCNU for patients with Dukes' C colorectal cancer

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A prospective controlled randomized trial testing adjuvant postoperative combination chemotherapy (5-fluorouracil, lomustine (CCNU) and vincristine) versus *no adjuvant therapy in patients operated on for Dukes' C colorectal cancer is reported. In total 334 patients aged less than 70 years were recruited: 205 patients with colonic and 99 with rectal cancer, but there were three protocol violations and these cases are excluded from further consideration. Twenty-seven patients had a limited resection of their cancer. After 5 years' follow-up there was no significant difference in the tumour-free survival rate or in the survival rate between the treated and control groups. Twenty-nine of the 147 patients who started chemotherapy discontinued this treatment because of side-effects, mainly from the gastrointestinal tract. In 30 patients treatment was discontinued because of recurrent disease. The conclusion is that systemic administration of combination chemotherapy for colorectal cancer after operation is not worthwhile in routine clinical practice.*

Keywords: Colorectal cancer, adjuvant chemotherapy, randomized study, 5-fluorouracil, lomustine (CCNU), vincristine

The results of surgery alone for patients with Dukes' C colorectal cancer are dismal. The 5-year crude survival rate for such patients with colon cancer is 37 per cent and with rectal cancer it is 25 per cent[1]. However, there are some studies indicating a somewhat improved survival prospect in recent years[2].

The number of published randomized studies assessing the value of adjuvant chemotherapy (liver infusion therapy excluded) in patients operated on for colorectal cancer is about 20, most of them being published in recent years. Each of these studies has shown no effects or a borderline effect on disease-free survival or overall survival rates in the total series or in subgroups. In a meta-analysis of trials employing regimens with 5-fluorouracil alone, the odds of death were reduced by 14 per cent in treated patients compared with control patients. This corresponds to an improvement in the 5-year survival rate of 5·7 per cent ($P = 0{\cdot}08$)[3].

In patients with colorectal cancer the combination of 5-fluorouracil and methyl-CCNU initially produced rather impressive results and objective tumour remission rates of 43 and 37 per cent were observed[4,5]. This motivated the Gastrointestinal Tumor Study Group (GITSG) in the USA and the Swedish Gastrointestinal Tumour Study Group to start trials with similar design. The Swedish study was launched in 1978. In the meta-analysis the combination therapy gave a 5-year survival rate benefit of 4·3 per cent ($P = 0{\cdot}06$)[3].

The Swedish trial is now at 60 months after randomization of the last patient and an evaluation of the study is indicated.

Patients and methods

In total, 334 patients with Dukes' C colorectal cancer have entered the study from 35 surgical departments in Sweden. The patients were recruited between 1979 and 1984. The protocol prescribed that the patients should be younger than 70 years of age. Mean(s.d.) age was 60(9) years and the sex distribution was 172 men and 162 women. Three patients were excluded (one received postoperative X-ray therapy and two had a Dukes' B colorectal cancer) Stratification of patients with regard to localization to colon and rectum is shown in *Table 1*

Twenty-seven patients, whose cancer in a retrospective analysis of operative and histopathological reports was not considered to have been treated by radical operation, are analysed in the evaluation of overall results but are excluded in subset analyses.

The patients were followed at 6-month intervals for 2 years and then at 12-month intervals for a further 3 years according to a work-up protocol including standard liver function tests, chest radiography, proctoscopy and barium enema. Recurrences that were verified between two intervals of follow-up were registered as having become manifest at the time of the subsequent follow-up.

Patients who died from colorectal cancer within the first 6 months of follow-up were considered to have had their recurrence at 3 months. When tumour recurrence or a new cancer was verified, no further follow-up was registered

Treatment

All patients were subjected to standard surgical procedures, i e right or left hemicolectomy, sigmoid resection, anterior rectal resection or abdominoperineal rectal resection

Patients allocated to therapy were given 5-fluorouracil (500 mg/m^2 body surface area intravenously on the first day after operation and 500 mg/m^2 orally on the following 4 days) On the first day in each cycle lomustine (CCNU, Lundbeck Ltd., Malmö, Sweden) (80 mg/m^2 orally) and vincristine (1·0 mg/m^2 intravenously) were given Cycle length was 42 days (6 weeks), i e. the next cycle was begun on day 43 The first cycle was started within 30 days of surgery. In total, eight cycles were given.

White blood cell count and platelet count were checked once a week. A white blood cell count within the range of 1·5–3·0 × 10^7/l or a platelet count of 50–99 × 10^9/l resulted in a 50 per cent dose reduction

Table 1 *Stratification of patients*

	Treatment	Control	Total
Radical treatment of the colon	103	102	205
Radical treatment of the rectum	43	56	99
Non-radical treatment of the colon and rectum	9	18	27
Total	155	176	331

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Table 2 *Side-effects causing discontinuation of chemotherapy*

	No
Gastrointestinal side-effects	21
Leucopenia and/or thrombocytopenia	6
Neurological symptoms	2

and a white cell count below $1\cdot5\times10^7$ and a platelet count below 50×10^9/l led to a 100 per cent dose reduction Gastrointestinal toxicity of grades 1 and 2 resulted in a dose reduction of 50 per cent and grades 3 and 4 led to a reduction of 100 per cent.

Control patients were not given any adjuvant chemotherapy.

Statistical methods

Survival time and time to recurrence were analysed by the life-table (actuarial) method. Differences between groups were evaluated by the means of Lee–Desu statistics (i.e. the generalized Wilcoxon test) All *P* values refer to two-tailed tests because a negative influence of therapy was possible

Results

Compliance

Seventy-six of 155 patients completed eight full cycles of treatment and, of them, eight patients completed treatment although recurrence was verified in one patient at 6 months and in seven at 12 months. Four patients refused treatment after randomization; two patients were not treated because of a long-standing postoperative complication (pneumonia and bladder dysfunction); and two never started treatment because of tumour progression before initiation. Forty-three patients completed between five and eight cycles and 28 patients completed between one and four cycles. Six patients refused to continue their chemotherapy after between one and four cycles and one discontinued treatment after seven cycles. Twenty patients discontinued their treatment before eight cycles because of recurrence at 6 months, and ten because of recurrence at 12 months. In 29 patients side-effects were the cause of discontinuation of treatment or significant dose reduction (*Table 2*).

One treated patient was lost to follow-up at 36 months and one control patient was lost at 48 months.

Survival

Eight patients died from causes other than colorectal cancer (three in the control group and five in the treated group).

There was no significant difference in survival between the treated (i.e. all patients selected for treatment) group and the control group in the total series and in patients in whom the tumour was localized to the colon or the rectum (*Figure 1*). The 5-year survival rate was 48 per cent for treated patients with colon cancer and 52 per cent for controls For patients with rectal cancer the numerical difference in the 5-year survival rate was 15 per cent, i.e. 34 per cent for control patients and 49 per cent for treated patients.

Tumour-free survival

The tumour recurrence rate within 5 years was 60 per cent in the treated group and 63 per cent in the control group (*Table 3*). The median tumour-free interval was not significantly different between the two groups. In the adjuvant-treated group of patients with rectal cancer the median tumour-free interval was 19 months longer than in the control group (36 months and 17 months respectively). For patients with rectal cancer the tumour recurrence rate within 5 years had borderline significance in that it was less in treated patients than in controls ($P=0\cdot07$) (*Figure 2*).

There were four new cancers in the control group and five in the treated group (*Table 4*). In one patient acute lymphatic leukaemia was diagnosed 36 months after therapy was started. This patient was given six full courses and two half courses of CCNU (total dose 500 mg/m^2).

Discussion

No study of adjuvant therapy has so far convincingly shown improvement in survival in patients with cancer of the colon or rectum. A level of effectiveness of a chemotherapy regimen in advanced disease close to 50 per cent seems desirable[6]. Unfortunately there is no such effective therapy for colorectal

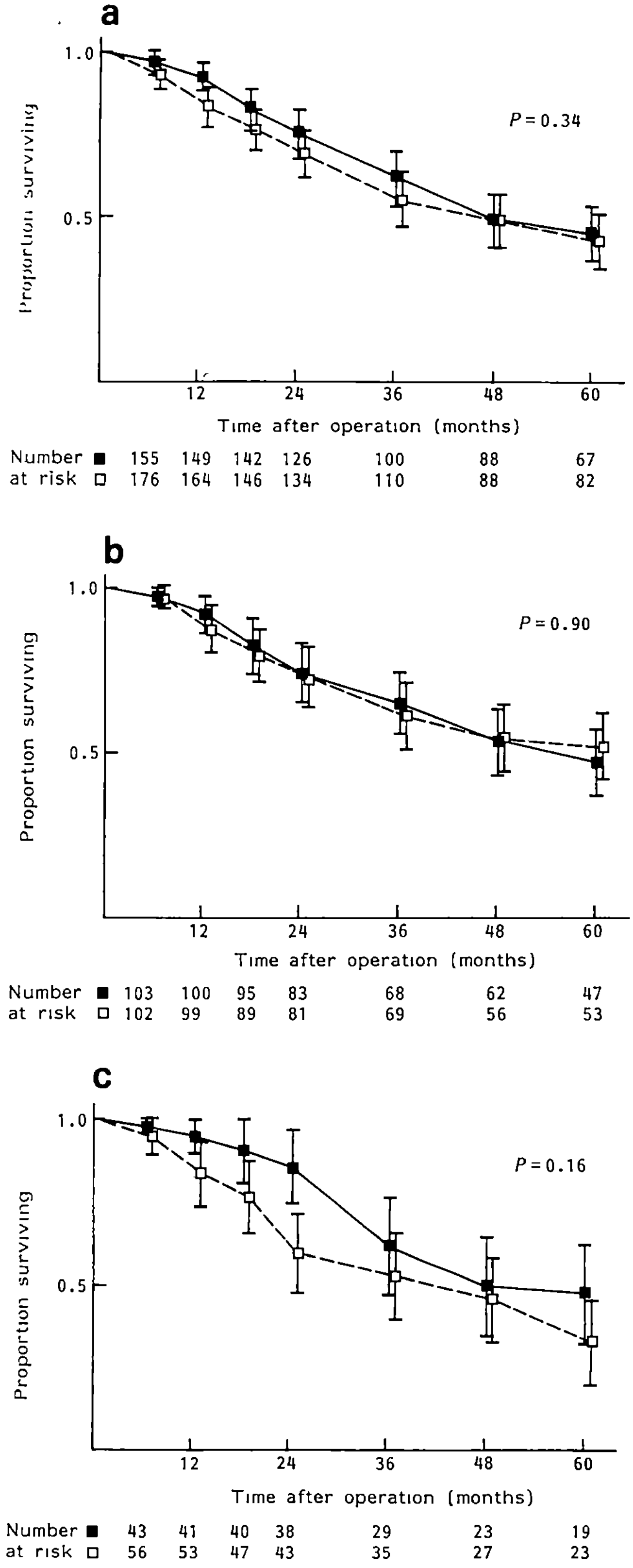

Figure 1 *Cumulative proportion surviving and 95 per cent confidence limits for patients with Dukes' C colorectal cancer subjected to adjuvant chemotherapy after surgery* (■) *and controls* (□), **a** *total series*, **b** *colonic cancer*; **c** *rectal cancer* ($P=0\cdot16$)

Table 3 *Percentage of patients with recurrence of colorectal cancer within 5 years of operation*

	Total	Colon	Rectum
Treatment	60	59	56
Control	63	55	71

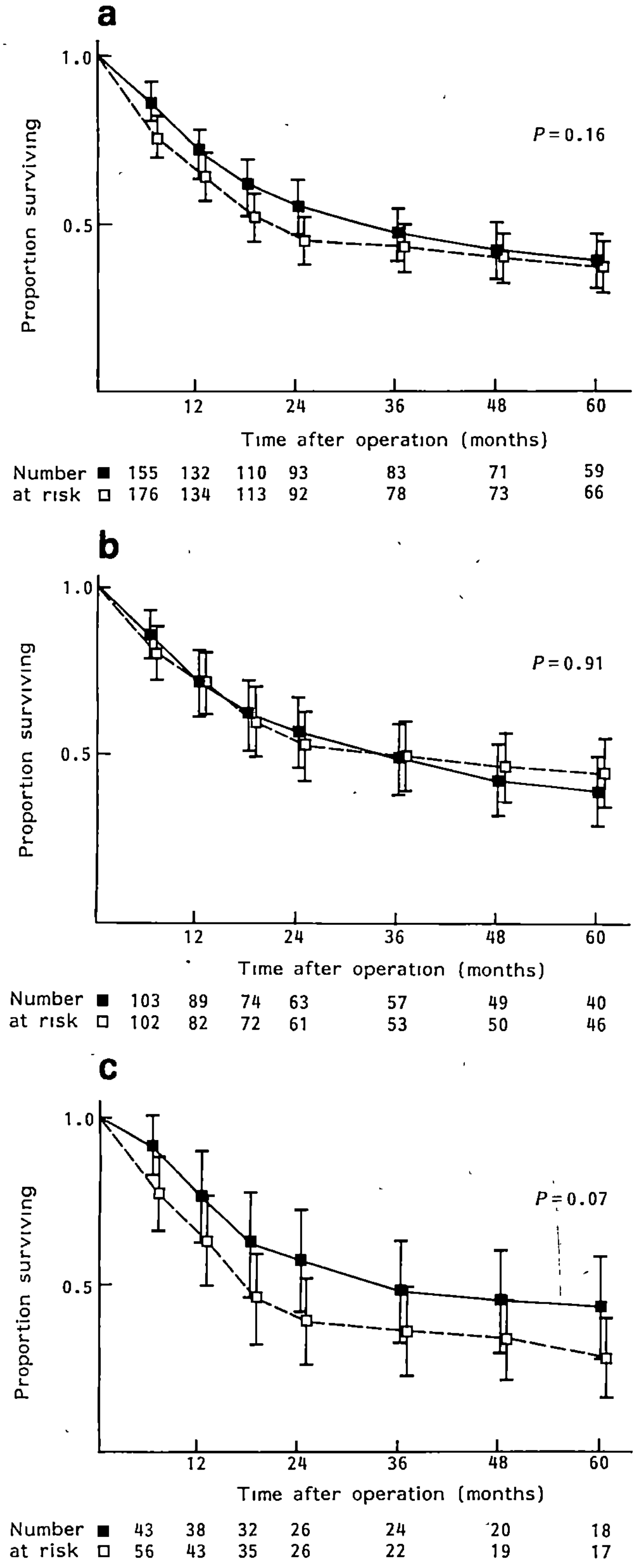

Figure 2 *Cumulative proportion tumour-free surviving and 95 per cent confidence limits for patients with Dukes' C colorectal cancer subjected to adjuvant chemotherapy after surgery* (■) *and controls* (□); **a** *total series;* **b** *colonic cancer;* **c** *rectal cancer* (P=0·07)

cancer and no patient with recurrence can be permanently cured by chemotherapy.

The good initial results experienced with 5-fluorouracil in combination with methyl-CCNU in patients with advanced disease[4,5] could not be repeated in further studies, which showed an objective tumour remission rate in the range of 20 per cent[7]. The present study, which concerns only patients with Dukes' C colorectal cancer who were aged less than 70 years, could not demonstrate any therapeutic effect of the adjuvant regimen. The remaining tumour burden after radical surgery may have been too heavy to be eradicated by the cytostatic adjuvant treatment.

In the subgroup of rectal cancer patients a borderline effect could be identified. In the previous Swedish study (testing oral 5-fluorouracil) a borderline effect was recognized in the subgroup of patients with Dukes' B tumours[8]. These could be chance findings, but if they can be reproduced and statistically verified in larger trials or in meta-analysis an improvement in the 5-year survival rate from 34 to 49 per cent is of clinical significance.

A 50 per cent 5-year survival rate for patients with Dukes' C disease is greater than is normally expected in this group of patients from a multi-institutional trial. A similarly improved survival rate was found in the GITSG trial from the USA[2]. It is not known whether this improvement is a result of improved surgery or improved staging.

The toxicity experienced by our patients was pronounced: 20 per cent of them discontinued treatment because of side-effects, mainly from the gastrointestinal tract and bone marrow. The risk of inducing blood malignancies with this kind of chemotherapy with nitrosoureas has also to be considered. One patient in this study developed acute lymphatic leukaemia. The relative risk of developing leukaemia is about 12-fold for patients with colorectal cancer treated with methyl-CCNU, especially for those who receive more than 1·0 g/m^2 and live for more than 4 years[9].

The present study and the previously published meta-analysis underline the fact that adjuvant chemotherapy administered systemically after operation for colorectal cancer is not worthwhile in routine clinical practice[3]. The results published by Taylor and collaborators concerning adjuvant portal infusion of 5-fluorouracil have opened new possibilities of attacking colorectal cancer with adjuvant regimens[10]. Because residual cancer cells may be stimulated to grow after removal of the main tumour, the intraoperative and immediate postoperative techniques of administering drugs may have special advantages[11]. Published results of postoperative treatment using 5-fluorouracil with levamisole (which may be regarded as a biological response modifier) also open new fields of adjuvant treatment which merit further exploration[12].

Table 4 *Timing of detection of non-colorectal cancer following surgery for colorectal cancer*

	Interval between colorectal surgery and detection (months)	Tumour location/type
Treatment group	12	Breast
	12	Uterus
	36	Leukaemia
	60	Breast
	60	Prostate
Control group	6	Kidney
	24	Lymphoma, stomach
	36	Lung
	60	Lung

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Value of retesting subjects with a positive Hemocсult® in screening for colorectal cancer

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Within a prospective randomized screening study for early detection of colorectal cancer with rehydrated Hemoccult II® test, the possibility of increasing the specificity of the test by retesting patients with an initially positive Hemoccult II test was investigated. Of those offered the test 3561 (62·6 per cent) returned it and it was positive in 210 cases (5·9 per cent). The repeat test was performed by 184 patients and was positive in 68 (1·9 per cent). All those with a positive initial test had rectosigmoidoscopy to 60 cm and a double contrast enema. A carcinoma was found in one in seven patients with a positive retest but in only one in 100 patients with a negative retest ($P<0.001$)*. The specificity of the test was, therefore, increased from 95 per cent to 98 per cent and the sensitivity was unchanged. Rescreening was offered at a later date and increased numbers were available: 7147 patients returned the test and 369 (5·2 per cent) were positive. The test was repeated in 360 patients and 118 (1·7 per cent) were positive. A colorectal neoplasm was found in one in three of those with a positive repeat test, compared with one in seven of those with a negative repeat test. In conclusion, screening for early detection of colorectal cancer with a rehydrated Hemoccult II test may be followed by investigation of only those patients with a positive retest. Such a procedure will reduce the work-load by 60 per cent without reducing sensitivity.*

Keywords: Colon tumour, screening

The guaiac test has been the most commonly used method in screening for colorectal cancer and, of this type of test, the Hemoccult II® (Smith Kline Diagnostic, Sunnyvale, California, USA) is the most widely used. The sensitivity of Hemoccult II may be increased by rehydrating the test before development, but the increased sensitivity is accompanied by a decreased specificity. The value of rehydration has been a matter of discussion and different approaches have been adopted in five current controlled randomized studies of screening for colorectal cancer. Rehydration has been abandoned in the Memorial Sloan-Kettering study and it has never been used in the Funen and Nottingham studies[1–3]. In Minneapolis and Gothenberg it was decided at an early stage to rehydrate, as many false negative tests were found among patients with carcinomas when unhydrated Hemoccult was used[4,5]

The purpose of this study was to determine whether retesting of patients with a positive Hemoccult II can increase the specificity of the test and keep the sensitivity unchanged or at least at an acceptably high level. Those with an initial positive test had rectosigmoidoscopy and a double contrast barium enema. Findings were correlated with the result of a repeated Hemoccult test.

Patients and methods

All 11 369 patients in Gothenberg born between 1 July 1925 and 31 December 1927 were randomly allocated to either a control group or a test group The 5692 in the test group were offered testing with Hemoccult II. Slides were mailed to the group who were asked to perform two tests on each of three consecutive stools, and to avoid fresh vegetables, fruit, meat, food made of blood and vitamin C for 2 days before and during the testing. The slides were sent back to the hospital and rehydrated before development All who had one or more positive among the six slides were asked to perform another test series with similar dietary restrictions These slides were also rehydrated before development. Those with positive tests in the initial series were invited for rectosigmoidoscopy and double contrast barium enema. They were asked if they had kept to the recommended diet.

Seventeen to 19 months later all those in the test group were invited to undergo rescreening Rescreening also included a screened group of 6204 patients born between 1 January 1923 and 30 June 1925 At initial screening those with a positive Hemoccult in this group were not retested and were therefore not included above. At rescreening, however, they were retested if positive. Altogether 11 691 patients were offered rescreening.

Correlation between the variables and the presence of neoplasms was tested with Fisher's test. All tests were two-tailed This investigation was part of a larger screening study for early detection of colorectal neoplasms with the aid of faecal occult blood testing[5]

Results

At the initial screening, 5692 patients were offered the test and 3561 (62·6 per cent) sent back the slides. Of these 210 (5·9 per cent) had a positive test and 184 (87·6 per cent) performed the repeat test. One hundred and seventy-five patients attended for investigations; nine refused to have a double contrast barium enema (*Figure 1*). Six more patients had complete investigation but did not perform a repeat test. Significantly more neoplasms, including carcinomas and adenomas with a diameter of at least 1 cm, were diagnosed in the group with a positive retest compared with the group with a negative repeat test ($P<0.001$). Carcinoma was found in one in seven of the former group compared with one in 108 of the latter group ($P<0.001$). The 95 per cent confidence intervals for diagnosis of an adenoma or a carcinoma in the two groups are shown in *Table 1*. Amongst the 3351 patients with a negative Hemoccult II, one carcinoma was found later. This tumour was diagnosed 17 months after primary screening at the time of rescreening.

At the time of rectosigmoidoscopy and barium enema all patients were asked if they had kept to the recommended diet

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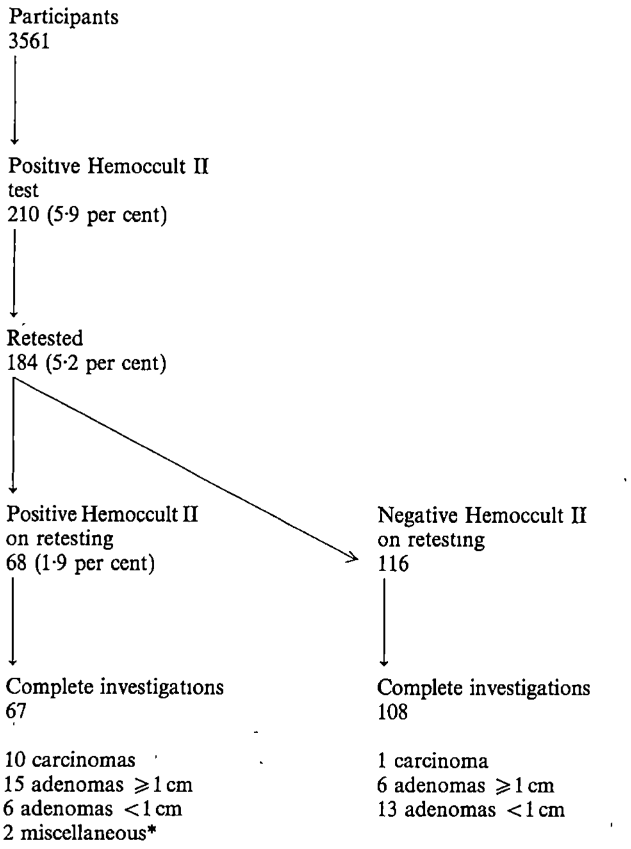

Figure 1 *Results of retesting patients with a positive Hemoccult II® test at primary screening. * One patient with inflammatory bowel disease and one with Oslow's disease*

Table 1 *Probability and 95 per cent confidence limit of probability of the diagnosis of colorectal carcinoma or neoplasm according to the result of retesting with Hemoccult II® All the subjects had a positive test at primary screening*

	Probability of carcinoma	95 per cent confidence limit	Probability of colorectal neoplasm	95 per cent confidence limit
Primary screening				
Second test positive	15	7–26	37	26–50
Second test negative	1	0·2–5	6	3–13
Rescreening				
Second test positive	4	1–9	22	15–31
Second test negative	0·1	0·1–4	6	4–11

before and during the sampling of faeces at the time of the first Hemoccult test. A negative Hemoccult on retesting occurred more often amongst those who had not kept to the recommended diet at the time of the first test ($P<0.02$).

In all, 11 691 patients were offered rescreening 17–19 months later, in exactly the same way as at the initial screening, and 7147 (61·1 per cent) sent back the slides (*Figure 2*). Of these, 369 (5·2 per cent) had a positive test and, of these, 360 (97·6 per cent) performed the repeat test. A full investigation was undertaken in 342 patients while 18 refused to have a barium enema (*Figure 2*). Nine more patients had complete investigations but did not perform a repeat test and one of these had a carcinoma in the sigmoid colon. The results of the complete investigations on the 342 patients are shown in *Figure 2*. Significantly more carcinomas and adenomas of at least 1 cm in diameter were diagnosed in the group with a positive repeat Hemoccult test compared with the group with a negative repeat test ($P<0.001$).

Observation of dietary restrictions at the first Hemoccult test did not influence the result of the repeated Hemoccult test.

Discussion

All ongoing large population studies of colorectal cancer in progress use Hemoccult as a screening tool. The sensitivity and specificity of this tool are of paramount importance to such screening programmes. The increased sensitivity obtained by rehydration is achieved at the cost of decreased specificity. In several studies the specificity has been considered to be so low that rehydration has been abandoned or has never been used[1–3]. In the present study, the specificity for colorectal neoplasms dropped from 99 per cent to 95 per cent after rehydration (1 year of follow-up). Macrae *et al.*[6] claimed that the decrease in specificity could be compensated for by using a restricted diet in which red meat and some types of fresh fruit and vegetables were avoided, and it was suggested that this concept should be tested in a larger field trial before definite conclusions could be drawn[6,7]. In the present study, 5·9 per cent had a positive test. The patients were asked if they had kept to the proposed diet and 24 per cent had not. Assuming that all these patients would have had a negative test at the primary screening if they had kept to the diet, the incidence of positive tests with rehydration should have been 133 of 3561 (3·7 per cent). This is two to three times more than that usually obtained with unhydrated Hemoccult tests in primary screening studies[2,3]. Thus, rehydration of slides from patients on a strict diet should result in more positive tests than if the slides are unhydrated. The corresponding figures on rescreening were 283 of 7147 (4·0 per cent), which is also two to three times higher than that obtained with unhydrated slides on rescreening[2,3].

There is no obvious explanation why 336 of 517 had a negative test on retesting. However, at primary screening

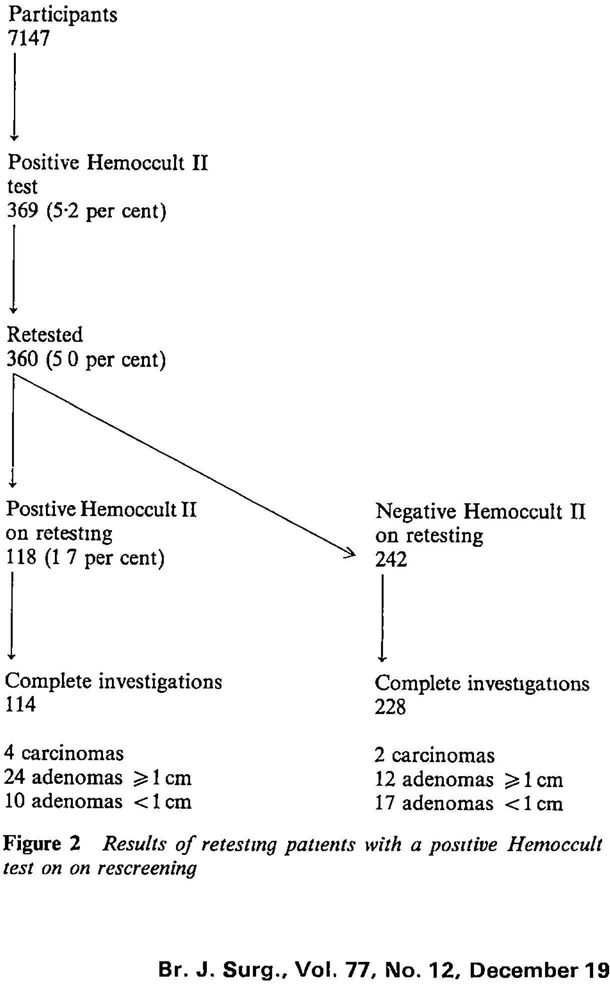

Figure 2 *Results of retesting patients with a positive Hemoccult II® test on on rescreening*

31 per cent of all those with a negative repeat test had not kept to the diet at the time of the first Hemoccult test, compared with 13 per cent of those with a positive repeat test. This might suggest that the diet influences the incidence of positive tests on rehydration only to some extent. A restricted diet seems to decrease the rate of positive tests but not to the same degree as unhydrated slides[8]. Therefore, dietary compliance does not fully explain why the positive rate of 5·9 per cent fell to 1·9 per cent at retesting. It is possible that patients were more likely to adhere to the dietary advice at the second test, although this information was difficult to ascertain at interview.

A way to increase the sensitivity of unhydrated slides has been suggested by Elliot *et al.*[9], who studied the effect of retesting of subjects with a positive Hemoccult. Ninety-nine patients of 3422 had a positive unhydrated test on their normal diet. The patients with a positive test underwent a second Hemoccult test over 6 days, while avoiding red meat and vitamin C (but not fresh fruit and vegetables). Thirty-two patients had a positive repeat test; 12 of these had a colorectal carcinoma and 11 had an adenoma. Thus, the number of positive tests was reduced, but the important issue of the possible number of subjects with carcinoma and adenoma and a negative second test was not addressed.

The effect of retesting was examined in the present study. All those who had initial screening and rescreening were retested, and a complete investigation was offered to all patients with a primary positive test. At the initial testing the percentage with a positive test dropped from 5·2 per cent to 1·9 per cent at the repeat test and from 5 0 per cent to 1·7 per cent on rescreening. The important issue is the number of neoplasms that would have been overlooked if only patients with a positive repeat test had been examined. At primary screening ten of 11 carcinomas were found in the group with a positive repeat test. Carcinoma was found in one in seven patients in this group, compared with one of 108 of those with a negative repeat test. The corresponding figures for adenomas with a diameter of $\geqslant 1$ cm were one in four and one in 18 respectively. The sensitivity for carcinomas at primary testing would have been almost unchanged if only those with a positive repeat test had been fully investigated, but the specificity would have increased from 95 per cent to 98 per cent.

Two carcinomas in six would have been overlooked if only those with a positive repeat test on rescreening had been investigated, although significantly more neoplasms were found in the group with a positive repeat test compared with those with a negative repeat test.

The increased specificity obtained when only those with a positive rehydrated repeat test are investigated is of great practical importance. The number of patients who have to be investigated will decrease by 60–65 per cent. At the primary screening the sensitivity obtained with rehydration was almost unchanged when only patients with a positive rehydrated repeat test were investigated.

In conclusion, this study on the sensitivity and specificity of the Hemoccult II test for screening for colorectal cancer has shown that it is possible to increase the specificity and still retain a high sensitivity if several adjustments to the methodology are undertaken. The rehydration procedure is necessary to reach an acceptable level of sensitivity for the Hemoccult test[5]. However, rehydration results in decreased specificity. It is possible to increase the specificity by a combination of dietary restriction and by retesting those with an initial positive test. Performed together, these adjustments result in an acceptable sensitivity and specificity for Hemoccult II in screening for colorectal cancer, making population screening both theoretically interesting (sensitivity of the screening method) and practically feasible (specificity of the screening method).

Acknowledgements

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Epidermal growth factor receptor expression in colorectal cancer

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Epidermal growth factor (EGF) receptor expression was estimated in 50 invasive human colorectal cancers using immunohistochemistry and the degree of expression was quantified from integrated optical density measurements on the stained sections. All tumours stained positively, but Dukes' C tumours exhibited significantly higher levels of receptor than either Dukes' A or B tumours. In addition, histologically high grade cancers expressed receptors more strongly than those of low grade. It is concluded that a high EGF receptor concentration is associated with poor prognostic factors in colorectal malignancy.

Keywords: Colorectal carcinoma, epidermal growth factor receptor

Epidermal growth factor (EGF) is a polypeptide which regulates cellular proliferation in a wide variety of tissues[1–3], but its precise role is not understood. The receptor for EGF is a 170 kDa phosphoglycoprotein located across the cell membrane[1], and the internal portion of this molecule bears a close relationship to the *v-erb-B* oncogene product[4]. It is thought that growth factors may be important in the proliferation of neoplastic cells and a number of human tumours have been shown to express the EGF receptor to a variable degree[5].

Colorectal carcinoma has been studied very little in this respect; EGF receptors have been demonstrated on neoplastic cells in this tumour[6,7] but their significance is unclear. In this study, using a mouse monoclonal antibody raised against the human EGF receptor, we have investigated the relationship between the degree of receptor expression and two well recognized prognostic factors in colorectal cancer: tumour grade and histological differentiation.

Patients and methods

Fifty patients with histologically proven invasive colorectal carcinoma were studied There were 26 women and 24 men whose ages ranged from 49 to 96 years. Immediately after resection, a portion was cut from the edge of each tumour and placed into liquid nitrogen for transport to the laboratory. Frozen sections (6 μm thick) were cut, air dried overnight, wrapped in aluminium foil and stored at −20°C

The primary antibody used to identify the EGF receptor on the sections was a mouse monoclonal immunoglobulin G2b raised against the human EGF receptor (Amersham International, Amersham, UK) using the receptor-rich vulval carcinoma cell line A431 as the immunogen[8]. The method used to visualize the bound antibody was the streptavidin–biotin system[9] as this has been previously shown to be the most sensitive technique for detection of EGF receptor[10]. The primary antibody was diluted 1:100 and the sections were incubated at room temperature for 60 min. This was followed by biotinylated rabbit antimouse immunoglobulin at 1·200, which was absorbed with 10 per cent human AB serum. Streptavidin complexed to biotinylated peroxidase was then used and the bound peroxidase was visualized using the diaminobenzamine/H_2O_2 reaction Endogenous peroxidase was not blocked, as preliminary investigations revealed this to be confined to granulocytes, which did not interfere with the interpretation of the tissue sections All stages of the staining routine were timed exactly to ensure uniformity throughout the series of tumours

Frozen sections of human placental tissue were used as positive controls and cytocentrifuged preparations of human lymphocytes served as negative controls[5,11]. Each stained slide of colorectal tumour was accompanied by an identical substitution control in which the primary antibody had been replaced by non-immune mouse immunoglobulin G (Sigma Chemical Company, Poole, UK)

Intensity of staining in the study sections was estimated using a flying-spot scanning microdensitometer (Vickers 85a, Vickers Instruments, York, UK) which provides integrated optical density measurements by automatically integrating absorbance measurements from a fine beam of monochromatic light (wavelength 466 nm) which rapidly scans a masked area of the specimen Each slide was studied with a mask area of 78·5 μm^2, chosen so that it could be easily located over a single cell Random readings were obtained from individual cells on each section, subtracted from the background reading and the mean value was taken as the integrated optical density value for the tumour The reproducibility of this technique was tested by obtaining 25, 50 and 100 readings from a single tumour and repeating this on three separate occasions. The mean values did not differ significantly between sessions when 50 or 100 readings were taken Fifty readings were therefore used routinely In addition to integrated optical density measurements the immunohistochemical staining was graded as 0, + or ++ on all sections.

Dukes' classification and histological grading was carried out by a pathologist (B.E.) who was not aware of the immunohistochemical assay results. A two-stage system of grading was used: well differentiated and moderately differentiated tumours were classified as low grade, and poorly differentiated or anaplastic tumours as high grade. This approach is more reproducible than more complex systems and it is known that well and moderately differentiated tumours behave in a similar way[12]

Results

Of the 50 tumours, eight were Dukes' A, 22 were Dukes' B and 20 were Dukes' C. In all cases, background and non-specific staining was minimal and positive staining for EGF receptor was confined to the neoplastic cells within the tumour. Integrated optical density measurements showed that all tumours exhibited EGF receptor expression although in five cases this was barely discernible by eye.

When the tumours were grouped according to Dukes' classification the more prognostically favourable tumours were associated with low integrated optical density values for the EGF receptor concentration (*Figure 1*). The mean(s.d.) value for Dukes' A tumours was 6·06(2·64); for Dukes' B tumours, 8·56(3·04); and for Dukes' C tumours, 14·15(4·36). All the differences between these means were statistically significant (*Table 1*). The tumours of low histological grade had a significantly lower mean EGF receptor concentration than high grade tumours (*Table 2*). Subjective grading of the EGF receptor staining gave similar results (*Table 3*).

Discussion

Quantification of antigen by immunohistochemistry is normally done using subjective histological grading systems, and is accordingly subject to interobserver and intraobserver variations[13]. Intensity of immunoperoxidase staining, however, can be measured by photometric techniques as the absorbance of light is directly proportional to the amount of the peroxidase reaction product. If monoclonal antibodies are used and assay conditions are held constant it is then justifiable to extrapolate

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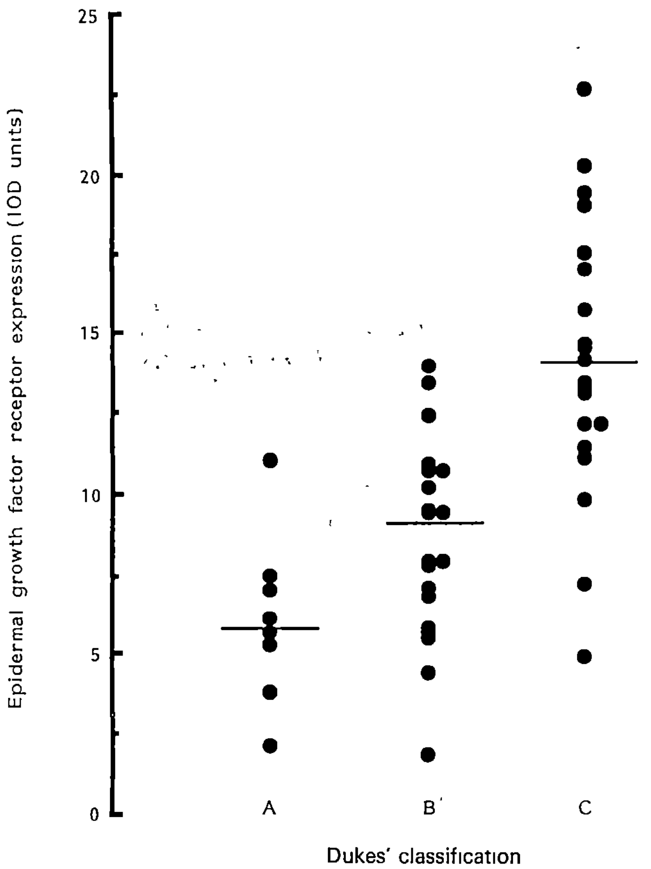

Figure 1 *Integrated optical density (IOD) values for epidermal growth factor receptor expression by human colorectal carcinoma as estimated by immunohistochemical staining Values grouped according to Dukes' classification*

Table 1 *Differences between mean integrated optical density values for epidermal growth factor receptor expression by colorectal carcinoma according to Dukes' classification*

Dukes' classification	Difference between means	95% confidence interval	P^*
A *versus* B	2·50	0·02–5·0	<0·05 >0·01
B *versus* C	5·58	3·3–7·9	<0·001
A *versus* C	8·08	4·7–11·6	<0·001

* Values calculated using Student's *t* test

from optical density measurements to the concentration of antigen recognized by the antibody[14].

In this study the technique has been used to quantify EGF receptor concentration in human colonic cancer. The monoclonal antibody used is a well characterized immunoglobulin which recognizes an epitope on the extracellular domain of the receptor[15], but does not compete with EGF for its binding site[16] It is therefore unlikely that the antibody is detecting an oncogene product, as *v-erb-B* encodes a truncated EGF receptor which lacks the external domain[4]. On the other hand, it is not clear whether the receptor identified by this means is functional, as the antibody gives no indication of ligand binding.

Accepting this limitation, the study shows that the concentration of EGF receptor tends to be higher in those colorectal tumours that are locally advanced and poorly differentiated This is in keeping with findings in other human tumours. Sainsbury *et al.* have established that, in breast cancer, EGF receptor expression is associated with poor differentiation, lack of oestrogen receptors and early disease recurrence and death[17–20]. Similarly, EGF receptor-positive bladder cancers tend to be invasive and poorly differentiated[21] and advanced gastric cancers are more likely to have receptors than are early tumours[7].

A major discrepancy between these results and those of others is the frequency of EGF receptor-positive cancers. All the colorectal cancers in this series had detectable receptor, albeit to a variable degree, whereas Sainsbury *et al.* found EGF receptors in only 32 per cent of breast cancers using both ligand binding and immunohistochemistry[17] In bladder cancer, 58 per cent of the specimens studied by Neal *et al.* were found to be EGF receptor positive[21] and Yasui *et al.* detected receptor in 72 per cent of colorectal cancers[7]. This may be related to the sensitivity of the streptavidin-biotin method[10] and to the ability of the scanning microdensitometer to detect low levels of staining which are difficult to appreciate without objective subtraction measurements of optical density. Simple subjective visual grading correlated well with prognostic factors and this may be of more practical value in view of the complex nature of the objective technique. EGF receptor expression appears to be a continuum rather than an 'all or none' phenomenon in colorectal cancer and this was only demonstrated by a sensitive, precise method.

The role of the EGF receptor in the behaviour of cancer is still obscure. Ligand binding studies in human tumours indicate that the receptor is capable of binding EGF, and its increased expression may be partly responsible for the rapid growth and consequent poor prognosis associated with locally advanced and poorly differentiated tumours. The EGF receptor, therefore, may have prognostic significance which could be used to supplement other factors in order to obtain a more precise prediction of outcome[22]. More exciting, however, is its possible influence over tumour growth. A fuller understanding of the interactions between the receptor, EGF and tumour growth factor-α might have important therapeutic implications in the future.

Table 2 *Differences between integrated optical density values for EGF receptor expression by colorectal carcinomas according to histological grade*

	Histological grading of colorectal tumour	
	Low grade	High grade
Number	39	11
Mean EGF receptor concentration (integrated optical density units)	9·2	14·5
Standard deviation	4·0	5·2
Difference between means	5·3	
95% confidence interval	2·4–8·2	
P^*	<0·001	

* Value calculated using Student's *t* test; EGF, epidermal growth factor

Table 3 *Relationship between subjective grading of epidermal growth factor receptor staining intensity and both Dukes' classification and histological grade*

	Grading of staining intensity	
	0/+	++
Dukes' classification		
A	8	0
B	19	3
C	5	15
	$\chi^2=22·48$ $P<0·001$	
Histological grade*		
High grade	3	8
Low grade	29	10

* High grade *versus* low grade, $\chi^2=8·26$, $P<0·01$

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Paraileostomy hernia: a clinical and radiological study

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Forty-six patients who underwent colectomy with end ileostomy for ulcerative colitis (n = *33*) *or Crohn's disease* (n = *13*) *have been reviewed for paraileostomy hernia (PIH) formation 1–16 years after surgery. PIH developed in 13 of these patients (28 per cent) and was not related to the original disease or excessive weight gain. Twenty-eight patients underwent limited computed tomography (CT) scanning of the stomal region. Eight of these had a clinically detectable PIH, which was demonstrated on CT. A further two patients had PIH demonstrated on CT which was not detected by clinical examination. The rate of PIH was similar where the stoma emerged lateral to the rectus abdominis muscle (six out of 16 patients, 37 per cent) to where the stoma emerged through the rectus (four out of 12 patients, 33 per cent). Recurrence following operative repair of PIH was common. PIH occurs more frequently than previously supposed. CT can detect PIH and may be useful in evaluating a patient with stoma-related symptoms for occult PIH formation.*

Keywords: Paraileostomy hernia, ileostomy, colectomy, complication, repair, computed tomography, imaging

The development of ileoanal pouch operations[1,2] has meant that a proportion of patients with ulcerative colitis do not require a permanent ileostomy. However, older patients and patients with Crohn's disease are not suitable for an ileoanal pouch procedure[3] and still require a permanent ileostomy. How the patient adapts to their stoma depends in part on the morbidity associated with the stoma. Paraileostomy hernia (PIH) formation is a potentially serious complication. Most commonly it presents with stoma care problems such as difficulty in fitting an appliance or leakage of ileal contents[4]. Other symptoms include pain and an unsightly bulge. Small bowel may become incarcerated in the hernia causing intestinal obstruction or infarction of the bowel[5].

The reported incidence of PIH is low, ranging from 0·8 to 10 per cent[6–11]. These figures are derived from reoperation rates and the true incidence of PIH formation may be higher because patients may not represent with a hernia or be aware of its presence. Large PIHs are easily detected on clinical examination but small hernias may be missed, especially in obese patients.

In this study we have reviewed ileostomy patients specifically for PIH formation. A subgroup of patients underwent computed tomography (CT) scanning of the stomal region to assess the usefulness of CT in the diagnosis of PIH.

Patients and methods

Sixty patients have undergone colectomy with end ileostomy for inflammatory bowel disease in our unit between 1972 and 1987; 46 patients were available for review. Of the 14 other patients, seven died between 1 month and 8 years after surgery, five were lost to follow-up and two patients have undergone ileorectal anastomosis. In each patient, the ileostomy was constructed using a standard technique described by Turnbull[12]. Special attention was paid to the size of the exit wound through the abdominal wall, which was limited to take the tips of two fingers at a maximum. The incision through the anterior rectus sheath was cruciate, extended through the rectus muscle and posterior rectus sheath as a simple stab procedure.

The age range of the patients was 14–76 years, with a median age of 40 years. There were 26 female patients. Thirty-three patients had ulcerative colitis and 13 patients had Crohn's disease. Follow-up ranged from 1 to 16 years, with a median follow-up of 6·5 years.

Patients were reviewed in the outpatient department by a single clinician (J.G.W.). Patients were questioned about stoma-related symptoms and any difficulties they were experiencing with their ileostomy appliance. Past history of surgery for PIH was noted. A PIH, defined as a palpable cough impulse in the paraileostomy region, was sought with the patient supine and erect after removal of the stoma appliance.

All patients were asked if they would undergo limited CT scanning of the region of their ileostomy. Twenty-eight patients agreed after the nature of the investigation had been explained. Patients were given dilute barium suspension to drink 1 h before the scan was performed. In four patients insufficient barium reached the distal small bowel loops and dilute barium was introduced into the ileostomy with a catheter. CT scans were performed on a Philips Tomoscan 350 body scanner (Philips, Eindhoven, The Netherlands) and 9 mm contiguous sections were performed through the ileostomy site. Scans were reviewed independently by both radiologists and were classified as positive if an extra loop of bowel was visible outside the abdominal cavity. The site of the emerging stoma in relation to the rectus abdominis muscle was also noted.

Results

PIHs have developed in 13 of the 46 (28 per cent) patients reviewed. The interval between surgery and development of a PIH ranged from 6 months to 14 years (median interval 2·5 years). The rate of PIH was not influenced by the underlying disease, being as common in patients with Crohn's disease (three out of 13 patients, 23 per cent) as in patients with ulcerative colitis (ten out of 33 patients, 30 per cent). After operation weight gain ranged from zero to 38 kg (median 7·7 kg). Patients who developed PIH gained a similar amount of weight (median 8·2 kg) to patients who did not develop PIH (median value 7·5 kg).

Three hernias were previously undetected and were discovered only when the patient was specifically reviewed for PIH formation. Four patients were asymptomatic, having easily reducible hernias which have not required surgical intervention. Two patients had local repairs of PIH performed by suturing the defect in the rectus sheath around the emerging stoma. Both of these recurred, 2 and 2·5 years later and the stoma was moved to the left iliac fossa in each case. No new PIH has

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developed in these two patients 2 and 2·5 years after this second procedure. Another patient had a local repair of her PIH reinforced with intraperitoneal prolene mesh, which remains intact 12 months later.

Six patients had their stomas transposed to the left iliac fossa as a primary procedure for PIH. Three developed PIH in the new site 2, 4 and 7 years after surgery. Two of these patients have not required further surgery, but the third had her stoma transferred back to the right side and a hernia developed in this site 1 year later. The three other patients who had their stomas transposed to the opposite side have not developed a second PIH, but have been followed for only 18 months.

Radiological study

Limited CT scans were performed of the stomal region of 28 patients at from 6 months to 14 years (median 6·8 years) after construction of their ileostomy. Satisfactory images were obtained in each case, allowing the defect in the abdominal wall, the emerging stoma, the subcutaneous tissues and any PIH to be defined (*Figure 1–3*). Both radiologists agreed in their interpretation of all CT scans.

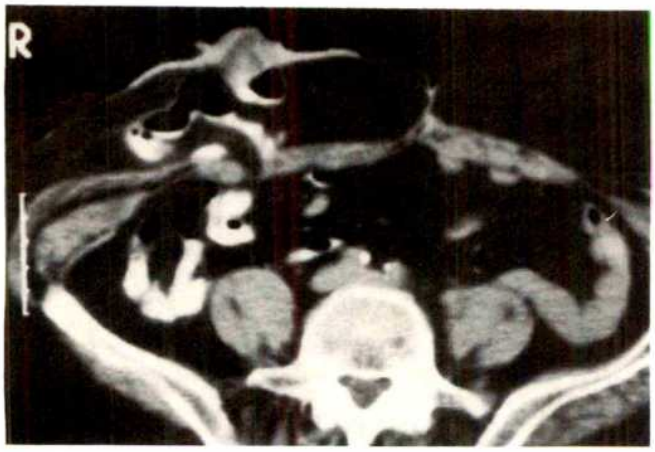

Figure 1 *Computed tomography scan of lower abdomen 2 years after proctocolectomy for Crohn's disease, showing a small paraileostomy hernia lateral to emerging stoma. Serial slices showed that the loop of bowel in the subcutaneous tissues was separate from the emerging stoma. The ileostomy is emerging through the rectus sheath and rectus abdominis muscle. This hernia was not detectable clinically*

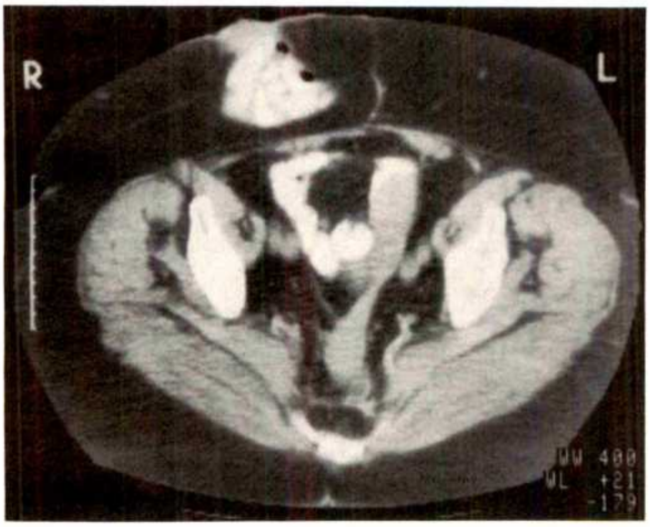

Figure 2 *Computed tomography scan of lower abdomen 4 years after proctocolectomy for Crohn's disease, showing a small paraileostomy hernia medial to the emerging ileostomy. The patient had gained 38 kg after operation and subcutaneous fat was 9 cm thick at the site of the stoma. This hernia was not detectable clinically*

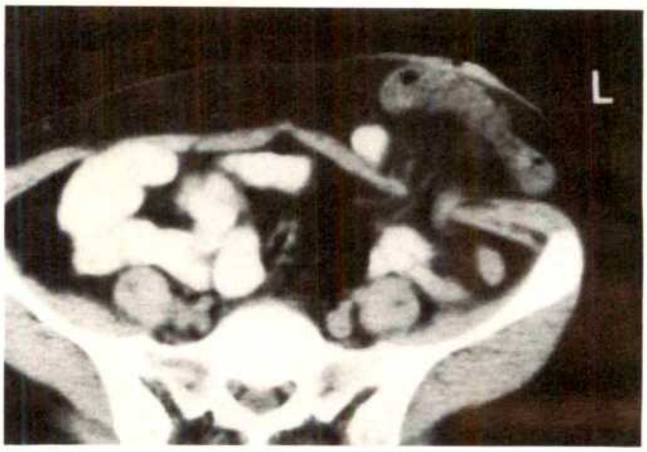

Figure 3 *Computed tomography scan of lower abdomen 10 years after proctocolectomy for ulcerative colitis. The stoma was moved to the left side 1 year after colectomy because of a parastomal abscess. There is a large paraileostomy hernia with multiple loops of bowel in the subcutaneous tissue. The ileostomy emerges from the abdomen just lateral to the rectus muscle. Note the scar in abdominal wall on right side at site of original ileostomy*

Ten patients were shown to have a PIH by CT scanning. The PIH was also detectable clinically in eight of these patients, but in two patients the PIH was detected only by CT scanning. One of these patients weighed 114 kg and had a 9 cm thick covering of subcutaneous fat in the parastomal region (*Figure 2*). Both patients had symptoms related to their stoma: leakage and difficulty in fitting an appliance in one and parastomal pain in the other. None of the 18 patients with normal CT scans of their ileostomy had any clinical evidence of a PIH.

The relationship of the emerging stoma to the rectus abdominis muscle and its sheath was studied. In 12 patients the stoma passed straight through the muscle and its sheath (*Figure 1*) and in the other 16 patients the stoma passed lateral to the rectus muscle (*Figure 3*). PIH formation was not influenced by the relationship of the emerging stoma to the rectus abdominis muscle, being equally common where the stoma passed through the sheath and muscle (four hernias, 33 per cent) as where the stoma exited lateral to the muscle (six hernias, 37 per cent).

Discussion

PIH formation is thought to be a much less frequent complication than paracolostomy hernia formation[1,3]. In this study we have shown that PIH formation is much commoner than was previously supposed.

The higher incidence of hernia formation in this study reflects the length of follow-up, patients being reviewed for up to 16 years after surgery. PIH may develop many years after stoma formation. Secondly, this study specifically reviewed patients for the presence of a PIH. Three patients were unaware of the presence of a hernia, which had not been noted at previous clinic visits. One-third of patients who developed a hernia did not require surgical intervention. Series which base the rate of PIH formation of reoperation rates will underestimate the true incidence of hernia formation.

For most patients a PIH is an inconvenience, making fitting of an appliance difficult with occasional leakage. The indications for surgery depend on the degree of difficulty the patient is experiencing, and many can control the hernia by wearing a special appliance with a belt. Strangulation of the small bowel is the most serious complication[5]. The risk is greater where the defect in the abdominal wall is narrow. Small intestinal obstruction with a tender lump in the peristomal region is highly suggestive of a strangulated PIH and is an absolute indication for surgery. Pain due to subclinical herniation occurs and may be misdiagnosed as adhesive obstruction or recurrent Crohn's disease.

The aetiology of PIH is uncertain. Obesity and wound infection have been suggested as possible aetiological factors[9,13,14]. Great emphasis has been placed on operative technique. Two factors are thought to be of particular importance: the size of the aperture in the abdominal wall and the relationship of the stoma to the rectus abdominis muscle. An opening of two finger breadths, or 2·5 cm in diameter, is thought to be optimum[9,12,15] and Todd[16] states that slight cyanosis of the stoma with oedema the following day indicates a correctly sized aperture. The hernias in this series developed in spite of attention to the size of the aperture.

It has been stated that a stoma placed through the rectus abdominis muscle has a lower chance of parastomal hernia formation than a stoma placed lateral to this muscle[12,17,18]. In the present study we did not find a difference in the rate of hernia formation between stomas placed in the two sites, and the relationship of the emerging stoma to the rectus muscle may not be as important as was previously thought.

The extraperitoneal colostomy described by Goligher is thought to have a lower incidence of hernia formation[9], although this has been disputed[13]. We have not found this technique satisfactory for ileostomy formation because of a tendency to obstruction where the ileum enters the peritoneal tunnel.

Various methods of repair of PIH have been described. These can be grouped into local repairs, with or without prosthetic material, and transposition of the stoma, with or without formal laparotomy. Satisfactory results of local repair by narrowing the defect in the abdominal wall muscles were reported by Weaver *et al.*[19] and Todd[20]. However, we have not found this technique to be satisfactory[21] and neither has Devlin[13]. Various techniques have been described of local repair reinforced by synthetic mesh[13,14,22]. Crohn's disease would make one wary of using synthetic material close to bowel.

Our favoured technique of repair is by translocation of the stoma to the other side of the abdominal wall. Others also advocate translocation[13]; however, as can be seen from this series, there is a high incidence of PIH in the new site. Techniques for translocation of the stoma without laparotomy have been described[23,24].

CT scanning is a novel method of assessing PIH formation. In this small study, two hernias were demonstrated by this technique which were not detected by clinical examination. CT scanning has also been used to demonstrate occult incisional hernias[25]. CT should be considered in a patient presenting with ileostomy-related symptoms and no obvious hernia to exclude an occult PIH.

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Effect of vaginal delivery on the pelvic floor: a 5-year follow-up

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We have studied the pelvic floor musculature and its innervation in 14 of 24 (58 per cent) multiparous women who had been recruited into a study of the effect of childbirth on the pelvic floor as part of a prospective investigation that began in 1983. These 24 women had all delivered by the vaginal route without forceps assistance. Five of the 14 had developed clinical symptoms of stress incontinence 5 years later; two of them had had a further uncomplicated vaginal delivery during this time. There was manometric and neurophysiological evidence of weakness because of partial denervation of the pelvic floor striated sphincter musculature, with pudendal neuropathy, which was more marked in those women with incontinence. These findings provide direct evidence for the hypothesis that pudendal neuropathy due to vaginal delivery persists and may worsen with time.

Keywords: Anorectal incontinence, anal sphincter, childbirth, postanal repair

In this report we describe a 5-year follow-up from a study of the effect of childbirth on the pelvic floor musculature that began in 1983. In our initial report[1] we described the changes found in the pelvic floor musculature and its innervation during the 2 month period after delivery in 122 women studied prospectively through pregnancy and delivery. We found that 80 per cent of primigravida sustained occult, but reversible pudendal nerve damage and that parity, forceps delivery, and increasing length of the second stage of labour were associated with more severe damage to the pelvic floor innervation[1,2]. Because of the potential importance of these findings in understanding stress incontinence we decided to reinvestigate some of these women and, since our clinical and electrophysiological evidence suggested that multiparous women are particularly likely to develop symptomatic incontinence[3], we chose to recall for study all the multiparous women from our previous investigation who had had an uncomplicated vaginal delivery. Since we have already shown that forceps delivery is associated with a greater risk of damage to the pelvic floor and its innervation[1,2] we decided not to include women from another group in our earlier study[1] who had experienced a forceps delivery.

Patients and methods

Letters were sent to all the 24 multiparous women who had taken part in our prospective investigation[1,2] of the effects of childbirth on the pelvic floor musculature 5 years ago, inviting them to attend for reinvestigation. These 24 women had all delivered by the vaginal route without forceps assistance. Fourteen (58 per cent) of these women agreed to return for this follow-up investigation Their ages ranged from 29 to 34 (mean 31·5) years. Four had had a further vaginal delivery in the 5 years since the previous study; in each case more than 2 years before the present investigation. None required forceps assistance, and none had any major complication during these births. Most of the remainder did not respond to our attempts to contact them at the addresses available to us, but four declined to attend for reinvestigation although they reported themselves free of sphincter disturbance The design of the previous study[1] was such that each of these women had been investigated at the end of the first trimester of pregnancy, 48 h after delivery, and again 2 months after delivery The present investigation thus represented a 5-year follow-up. Twenty nulliparous women aged 19–28 (mean 24) years served as control subjects

The investigations used in our studies of the pelvic floor have been fully described in other reports[1,4]. In each woman, the resting anal tone and maximal voluntary contraction pressure in the anal sphincter zone was measured using a water-filled microballoon system according to the standard protocol developed at St Mark's Hospital[5] The position of the perineal plane was assessed in relation to the plane of the ischial tuberosities, both at rest and during a maximal defaecation strain, using the St Mark's perineometer[6]. The fibre density, representing the mean packing density of muscle fibres innervated by a single motor axon, was measured in the external anal sphincter muscle using single fibre electromyography[7]. The mean pudendal nerve terminal motor latency was measured, using the transrectal method developed at St. Mark's Hospital[8] All these women had been investigated with these techniques during the earlier stages of this study, although the mean pudendal nerve terminal motor latency had not been measured antenatally, and single fibre electromyography was not used at the first post-natal investigation 48 h after delivery[1]. The reproducibility of these tests has been validated in an interobserver study[9]

The Wilcoxon rank sum test was used to test for differences between the sets of data. The study was carried out with the approval of the Combined Ethical Committee of St. Mark's and St. Bartholomew's Hospitals, and with the fully informed consent of all the women who took part.

Results

The mean(s.d.) fibre density in the external anal sphincter muscle, calculated during single fibre electromyographic studies in the 14 multiparous women studied, was increased both 2 months after delivery (1·59(0·25)) and 5 years after delivery (1·82(0·47)) compared with the fibre density in these same women calculated at the antenatal examination 6 months before delivery (1 42(0·21); $P<0{\cdot}01$), and with the group of 20 nulliparous, age-matched control subjects (1 30(0·16); $P<0{\cdot}01$) (*Figure 1*). The mean pudendal nerve terminal motor latency, calculated separately for the right and left sided investigations, was increased both 48 h after delivery (2·23 ms(0·29) right; 2·37 ms(0·67) left; $P<0{\cdot}01$) and 5 years after delivery (2·25 ms(0·18) right; 2·30 ms(0·50) left; $P<0{\cdot}01$) (*Figure 2*) compared with the nulliparous controls (1·90 ms(0·20); combined right and left mean pudendal nerve terminal motor latency data), although the mean pudendal nerve terminal motor latency in these multiparous women 2 months after delivery 5 years previously[1] was in the normal range (1·97 ms(0·12) right; 1·89 ms(0·22) left). The mean anal pressure during maximal voluntary contraction was lower 48 h after delivery (47·3 cmH_2O(13·0)), 2 months after delivery (50·0 cmH_2O(30·0)), and 5 years after delivery (50·0 cmH_2O(29·9)) compared with the antenatal measurements in the same subjects (73·5 cmH_2O(31·1); $p<0{\cdot}01$) and with the nulliparous controls (104·7 cmH_2O(50 5); $P<0{\cdot}01$) (*Figure 3*). The mean position of the plane of the perineum with

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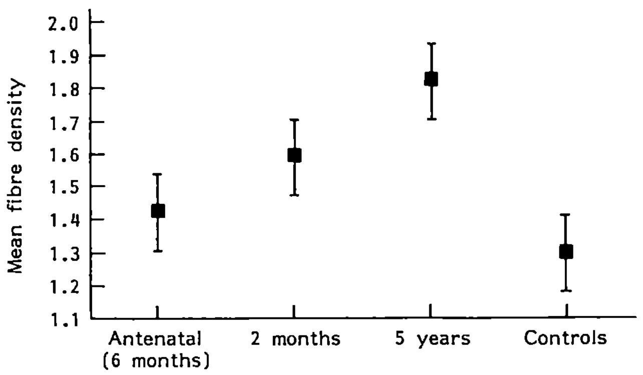

Figure 1 *Single fibre electromyography. Mean fibre density (bars represent ±1 s.e.; see text for s.d.). There was an increase in mean fibre density in the 14 multiparous subjects during the 5 years following entry*

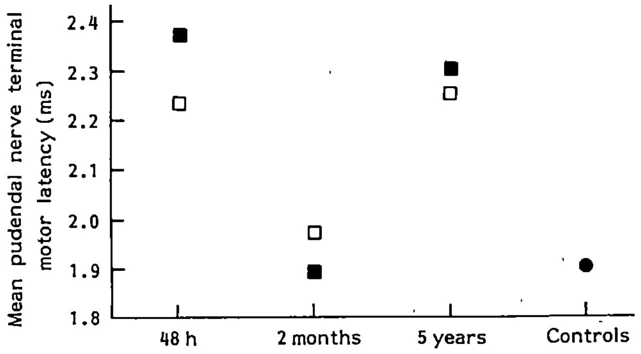

Figure 2 *Pudendal nerve terminal motor latency (standard errors omitted for clarity; see text for s.d.). Mean pudendal nerve terminal motor latency was increased at the 5 year follow up. The control value (●) represents the combined mean of the right (☐) and left (■) data, which were identical in value*

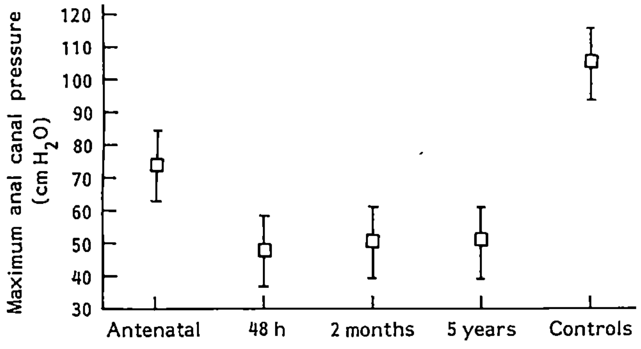

Figure 3 *Anal canal pressure during a maximal squeeze contraction (bars represent ±1 s.e.; for s.d. see text). These multiparous women generally showed lower maximal anal canal pressures than the age-matched control group, and the anal canal pressure did not return to the level recorded at the first examination*

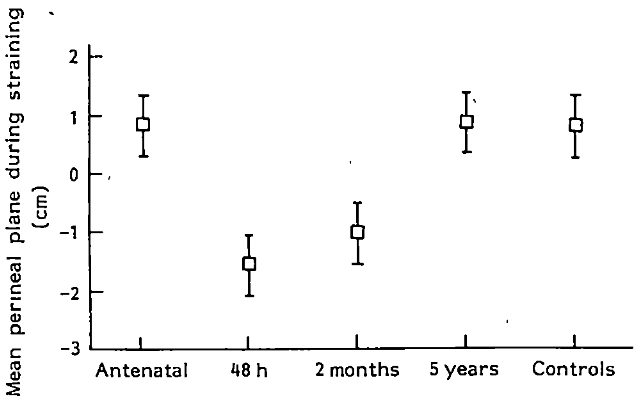

Figure 4 *Mean position of the perineal plane during a maximal straining effort (bars represent ±1 s.e.; for s.d. see text)*

respect to the plane of the ischial tuberosities was lower 48 h after delivery (−1·55 cm(0·51)) and 2 months after delivery (−1·02 cm(0·48)) compared both with the measurements made before delivery in the same women (+0·82(0·57); $P<0·01$) and with the nulliparous control subjects (+0·80 cm(0·70); $P<0·01$). Five years after delivery, however, the perineal plane (+0·87 cm(0·66)) was similar to that found in the antenatal assessment of the same women and in the nulliparous controls (*Figure 4*). Analysis of the results in individual women showed that the fibre density in the external anal sphincter muscle was increased in five women, and that these five women also had increased mean pudendal nerve terminal motor latency measurements; these five women had developed symptomatic stress urinary incontinence during the 5 year period between the current investigation, and the earlier study. Three of these women were unable to control flatus. There was no clear relation between additional vaginal delivery and these findings since two of the women who had developed stress incontinence had had a subsequent vaginal delivery, and two had not. In three women the pudendal nerve could be stimulated only on one side of the pelvis. In these three women this nerve had proved impossible to stimulate 48 h after delivery.

Discussion

This investigation, carried out prospectively in 14 of 24 (58 per cent) multiparous women recruited into our study of the effect of childbirth on the pelvic floor striated sphincter musculature, shows that occult damage to the pudendal innervation of the external anal sphincter muscle persists, or may be more marked, 5 years after the initial observation. The results were not influenced by the four women who had an additional vaginal delivery in the intervening 5 years because two of these four women had developed stress incontinence and two had not. Most of the 42 per cent of patients who were not followed up proved untraceable and their current clinical status is unknown to us.

The continued presence of pudendal nerve dysfunction and the development of weakness of the perineal musculature, as shown by anal manometry, is consistent with the finding that denervation of the pelvic floor musculature is the major factor in the pathogenesis of stress incontinence of urine and faeces. Denervation of the pelvic floor striated sphincter musculature is a gradually progressive phenomenon that is usually initiated by damage to the innervation of the pelvic floor muscles caused during vaginal delivery[1,3,10–13]. Urinary incontinence of stress type had developed in five women in the 5 year period following the previous investigation, and in three of these there was inability to control flatus adequately. In these five patients this incontinence was associated with abnormal fibre density measurements in the external anal sphincter and with increased mean pudendal nerve terminal motor latency. We have previously shown that the perineal nerve terminal motor latency is increased when the mean pudendal nerve terminal motor latency is abnormal[9,10], and that stress urinary incontinence is closely associated with an increased perineal nerve terminal motor latency[11,12]. Asymmetrical involvement of the pudendal nerves in patients with neurogenic anorectal incontinence is a common feature of this disorder[14]. Similar asymmetrical involvement of the pudendal nerves was found in the 14 women we have studied at follow-up, in three of whom it proved impossible to stimulate the nerve on one side of the pelvis. Wunderlich and Swash[15] showed that, after section of one pudendal nerve, extensive reinnervation of the denervated hemi-external anal sphincter muscle develops from the contralateral nerve, a mechanism that is probably an important compensatory process in this circular muscle. Increased perineal descent on straining is almost always found after vaginal delivery, but tends to return to normal during the subsequent 2 months[1]. The perineal plane was normal in 11 of the 14 women followed up in this study, but the three in whom it was abnormal had all developed stress urinary incontinence. This association of stress incontinence with perineal descent is consistent with the concept that perineal descent is a sign of pelvic floor weakness[6,11,13]. Although age effects, and possibly also menopausal effects[16,17], are relevant in considering the pathogenesis of incontinence in general, in the young population of women forming the basis of our study this factor can be discounted.

We conclude that pudendal nerve damage with partial reinnervation of the external anal sphincter muscle persists, and may become more marked, 5 years after vaginal delivery. This abnormality is associated with the development of stress incontinence of urine and faeces. These observations indicate the potential importance of devising methods to prevent damage to the pelvic floor innervation during childbirth, and further suggest that detection of an underlying abnormality in pelvic floor innervation is an important part of the surgical assessment of patients before pelvic floor surgery. Our follow-up represents a relatively small number of patients; consideration of the possible reasons for continuing damage to the pelvic floor innervation requires a much larger prospective study. The evidence available from our studies of this question[1–3,6–8,10–14] suggests that it is due to the functional effects of the original injury, together with other factors especially, in some subjects, an abnormal straining pattern of defaecation with pelvic floor descent leading to stretch-induced damage to the pelvic floor innervation during defaecation. In older subjects the development of lumbosacral spondylosis may also be relevant[11,17]. However, in the present investigation abnormal perineal descent on straining was the only clinical factor that seemed to be related to the progression of pelvic floor denervation and reinnervation, associated in five women with stress incontinence of urine and in three of these with loss of control of flatus, that we observed during the 5-year period of follow-up.

Acknowledgements

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Disordered colorectal motility in intractable constipation following hysterectomy

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Colorectal and anal sphincter motility and electrophysiology were investigated in 14 women with profound constipation following hysterectomy and compared with an asymptomatic group of control subjects. Twelve patients complained of significant urinary symptoms. No differences in the motor function of the anal sphincters were detectable. The latency of the pudendoanal reflex was unchanged after hysterectomy. Proctometrograms demonstrated significantly increased rectal volumes and compliance in the hysterectomy group together with deficits of rectal sensory function. In the basal state a significant proximal-to-distal sigmoid colon motility gradient existed only in the control group. Following stimulation with Prostigmin®, this gradient was enhanced in the control group but paradoxically reversed in the hysterectomized patients, thus constituting a functional obstruction. Denervation supersensitivity was demonstrable in two patients tested with carbachol provocation but not in control subjects. These findings suggest dysfunction in the autonomic innervation of the hindgut in some patients who had undergone hysterectomy, resulting in severe constipation.

Keywords: Autonomic nerves, constipation, hysterectomy, denervation hypersensitivity

Hysterectomy is a frequently performed operation with few untoward sequelae and the results of surgery are usually judged with regard to the pelvic pathology for which the procedure was undertaken. Descriptions of functional side-effects following the operation have been mainly confined to the lower urinary tract[1–7] and were initially attributed to coincidental urinary tract infection or alteration in the support of the bladder offered by the uterus and pelvic floor. Injury to the innervation of the urinary bladder and its sphincters, however, may play an important part in the development of these complications[8,9].

This study was prompted by the observation that some patients referred for investigation of intractable constipation appeared to have developed this problem following pelvic surgery and related their late-onset constipation to hysterectomy. These patients appear to represent only a very small proportion of women who undergo the operation for various disorders. In the light of previous observations of urological[1,2,4–8,10], sexual[11] and colorectal[12–14] dysfunction following some forms of pelvic surgery, the motility of the sigmoid colon, rectum and anal sphincters was studied under basal and stimulated conditions to explore the physiology of constipation following hysterectomy.

Patients and methods

Formal approval was obtained from the ethical committee of the North Lothian District, Lothian Health Board, Edinburgh, in June 1985 for the investigations described in this study. Informed consent was obtained from all participants.

Physiological studies of the motility of the sigmoid colon, rectum and anal sphincters were performed in 14 women suffering from intractable constipation following hysterectomy and were compared with results from an asymptomatic group of matched control subjects. The mean age of the patients with constipation was 36·8 years and the mean duration of symptoms was 6·1 years. All patients related the onset of their severe constipation to hysterectomy. This had been performed via the abdominal route in 12 patients and vaginally in two, all for benign disease. Oophorectomy had not been performed in any of the patients. The frequency of defaecation ranged from one spontaneous bowel motion per week to no bowel motion in a whole month without the use of enemas. Dietary and drug adjustments to relieve the constipation had proved unsuccessful. Twelve of the patients had troublesome urinary symptoms necessitating urodynamic assessment. These comprised stress incontinence in five patients, frequency in three, urge incontinence in two and atonic retention in two.

Fourteen approximately age-matched women with minor anorectal conditions gave consent for similar studies. None of them had suffered from constipation.

Radiology

Double contrast barium enemas were performed in all the patients. The control group was not subjected to this investigation.

Manometry

The manometric studies were conducted in a fasted state in the morning, the patients having been given the opportunity to empty the bowel beforehand. No other bowel preparation was used. All except necessary oral medications were withdrawn 48 h before the motility investigations. Anal sphincter manometry was performed using conventional methods[15] to measure basal and squeeze pressures, sphincter length and the presence of the rectosphincteric reflex. Proctometrograms[16] were obtained in all patients to measure volumes and pressures at sensory threshold, constant sensation and maximal rectal distension. Rectal compliance was calculated from the trace obtained as ml/cmH$_2$O. Motility of the sigmoid colon was monitored by means of a triple lumen soft-rubber tube (internal diameter of each lumen was 1 mm) placed via a sigmoidoscope, the side openings lying at a distance of 15, 20 and 25 cm from the anal verge. The water-filled tubes were connected via external pressure transducers to a multichannel chart recorder, the system being regularly flushed throughout the test. Basal motility index was calculated from the tracings obtained over a 20 min period using Connell's method[17]. The heights, waves and frequency of the motility traces were converted to x and y co-ordinates by the use of a computer (Hewlett-Packard 85 with Summagraphics attachment, Hewlett-Packard, West Lothian, UK) for mathematical computation of the motility indices. Prostigmin® (neostigmine; Roche Products Ltd., Welwyn Garden City, UK) was then injected subcutaneously in a dose of 0·01 mg/kg and the motility was further monitored over a similar period of time, beginning 5 min after the Prostigmin injection. Two subjects in each group also underwent motility studies following a subcutaneous injection of carbachol (500 μg).

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Table 1 *Manometric and electrophysiological data in 14 hysterectomized and control subjects*

	Control	Hysterectomy	P
Length of anal high pressure zone (cm)	2·7(0·3)	2·6(0·5)	>0·05
Maximum anal basal pressure (cmH$_2$O)	92·3(5·1)	91·4(5·6)	>0·05
Anal pressure response to cough (cmH$_2$O)	106(26)	89(31)	>0·05
Maximum anal squeeze pressure (cmH$_2$O)	120(16)	108(36)	>0·05
Rectal sensory threshold (mlH$_2$O)	224(120)	420(80)	<0·01
Rectal constant sensation (mlH$_2$O)	306(68)	452(180)	>0·05
Rectal maximal tolerable volume (mlH$_2$O)	478(86)	680(120)	<0·01
Rectal compliance (ml/cmH$_2$O)	9·2(4·3)	24(12)	<0·01
Latency of pudendoanal reflex (ms)	37·2(5·8)	39(6·2)	>0·05

Values are mean(s.e.m.)

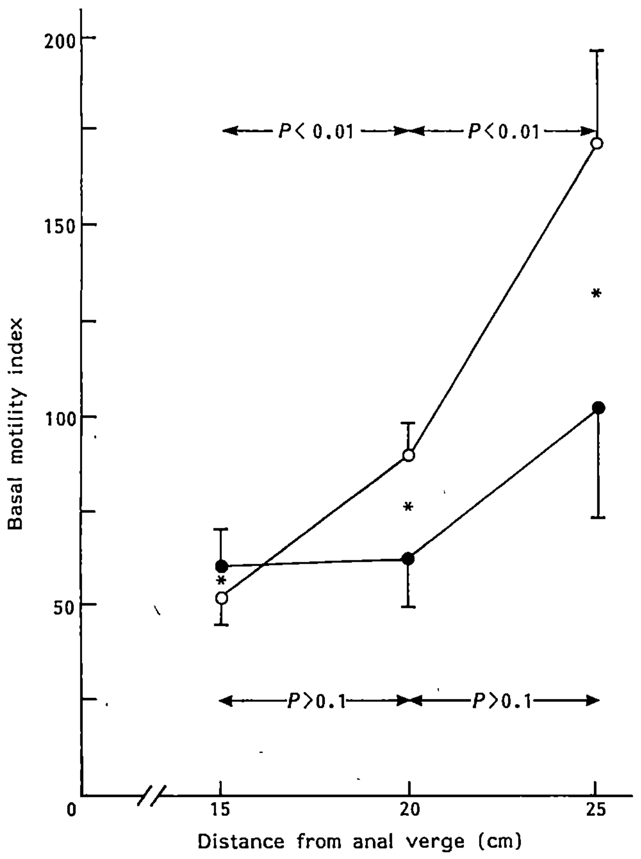

Figure 1 *Basal colonic motility in 14 hysterectomized patients* (●) *and in controls* (○) *P>*0·1*

Electrophysiology

Seven patients and all controls underwent measurement of the latency of the pudendoanal reflex as an index of the integrity of the conus medullaris and its somatic outflow to the anal sphincter musculature[18]. The phenomenon of anismus was tested for in all subjects by recording the integrated electromyograph of the sphincter musculature with an anal plug electrode, and an anismus index was calculated[19].

Statistics

Statistics were performed using Wilcoxon's non-parametric analysis. Paired comparisons were made for the motility indices before and after administration of Prostigmin, the remaining data being analysed by the unpaired formula.

Results

Radiology

Double contrast barium enemas showed no abnormality in 11 patients, megacolon in one and a redundant colon in two patients.

Manometry

Table 1 compares the manometric and electrophysiological data between the two groups. There were no significant differences in sphincter function. Rectal compliance and volumes appeared significantly increased in the group that had undergone hysterectomy, some of these patients demonstrating severe defects in rectal perception to distension.

The studies on colonic motility gave the following three observations. First, in the basal or resting state a significant proximal-to-distal motility gradient was demonstrable in the control group but not in the hysterectomy group (*Figure 1*). Second, following stimulation with Prostigmin the proximal-to-distal motility gradient was further accentuated in the control group, increases in motility occurring at all three sites. In the hysterectomy group, a lesser increase in motility occurred and there was a paradoxical reversal of the motility following stimulation in this group, i.e. there was now a significant distal-to-proximal motility gradient (*Figure 2*). The cumulative motility increase with Prostigmin was significantly less in the hysterectomy group (*Figure 3*). Third, a qualitatively hypersensitive motility response to carbachol was demonstrable in the two patients with constipation but not in the control subjects (*Figure 4*).

Electrophysiology

The pudendoanal reflex latency was delayed in one patient although statistically the differences between the two groups were not significant (*Table 1*). There was no difference in the anismus index between the two groups.

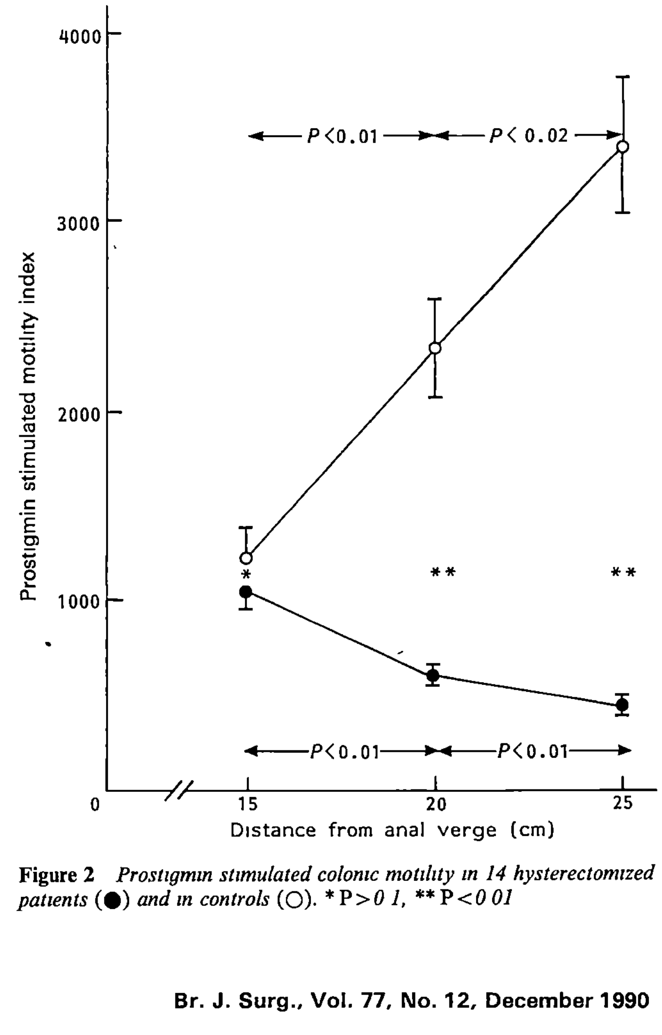

Figure 2 *Prostigmin stimulated colonic motility in 14 hysterectomized patients* (●) *and in controls* (○). *P>*0·1*, **P<*0·01*

Discussion

Dysfunction of the urinary bladder following pelvic surgery, including hysterectomy, has been previously documented[1,2,4–6,10]. Other forms of pelvic surgery may lead to sexual dysfunction, presumably secondary to autonomic nerve damage[11]. The clinical observation that a small proportion of women develops intractable constipation following hysterectomy has been substantiated by a larger clinical study[14]. The parasympathetic innervation of the urinary bladder, left colon and rectum derives from sacral segments S_2, S_3 and S_4 via the pelvic nerves[11,20–24]. From the inferior hypogastric plexus nerve fibres run forward to innervate the bladder and upwards and out of the pelvis to innervate the rectum and left colon[11,25,26]. This innervation is of paramount importance in the co-ordinated contractions of the smooth muscle of the bowel and bladder. It also carries the sensory fibres to these viscera. It is conceivable that damage to this autonomic innervation during pelvic surgery may result in functional disorders of the colon.

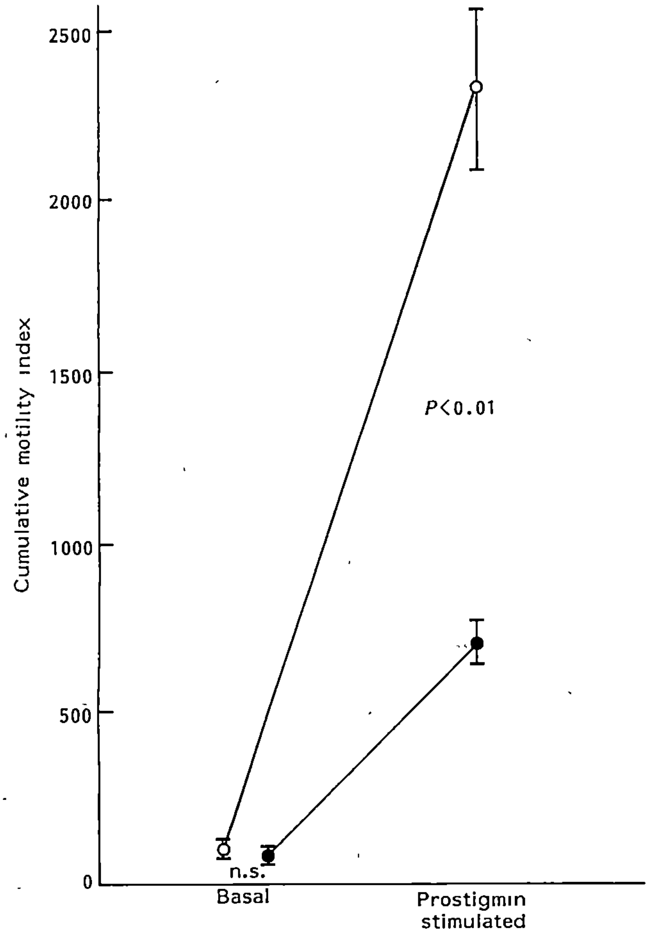

Figure 3 *Cumulative basal and Prostigmin stimulated colonic mobility in 14 hysterectomized patients (●) and in controls (○); n.s., not significant*

Long and Bernstein discussed the possible sites of nerve injury during pelvic surgery, with particular reference to sexual dysfunction[11]. The inferior hypogastric (pelvic) plexus in the female is placed on the side of the rectum, uterine cervix, vaginal fornix and posterior aspect of the urinary bladder and extends into the base of the broad ligament of the uterus[25]; it is presumably susceptible to injury during hysterectomy. Adamson and Aird[27] produced experimental megacolon in animals by cutting the pelvic nerves. White *et al.*[28] described severe bladder and bowel dysfunction in patients with acute damage to the sacral segments of the spinal cord or the lower sacral nerves, with the development of an atonic bowel. Scott and Cantrell[12] demonstrated functional changes in the colon following section of its pelvic parasympathetic nerve supply in the dog. These observations and those of the present study suggest that constipation in this group of patients may occur as a result of incidental injury to the autonomic parasympathetic innervation of the left colon and rectum. This conclusion is substantiated by abnormalities of bladder function noted in the same patients.

The response to carbachol is typical of denervation supersensitivity[29–32]. The motility response to Prostigmin is diminished but not abolished. This would be expected in an organ with incomplete damage to its innervation. The paradoxical reversal of motility in the constipated group following Prostigmin stimulation is difficult to explain but constitutes a functional obstruction at the rectosigmoid level. Presumably, either the proximal extrinsic innervation is more susceptible to damage and/or is more sensitive to the same injury compared with the innervation to the rectum. There is good anatomical evidence to suggest that rectal motility is more

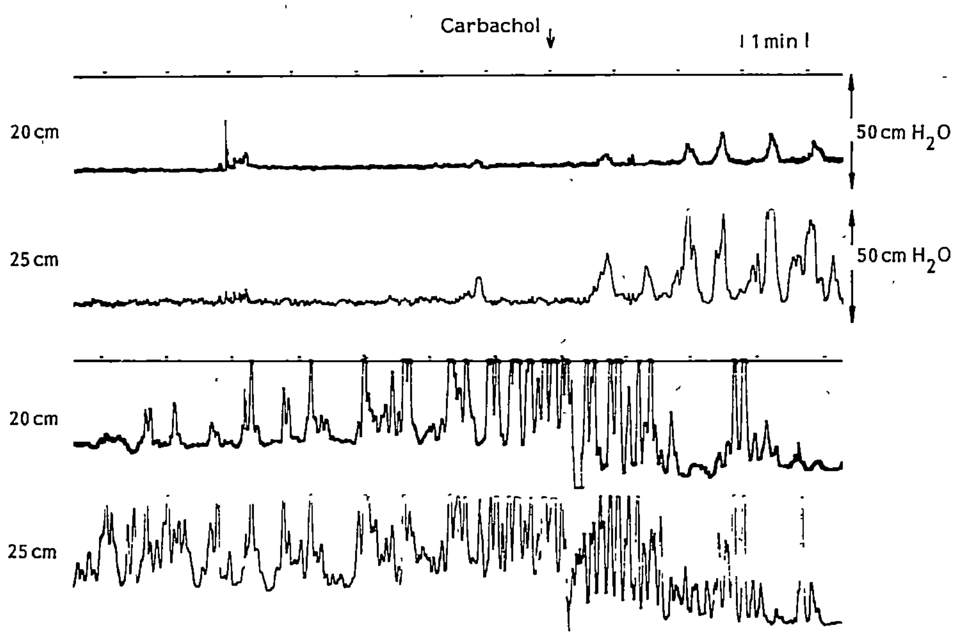

Figure 4 *Hypersensitive response to carbachol in a hysterectomized patient with severe constipation*

dependent on its intrinsic innervation than the more proximal colon which has a considerable extrinsic nerve supply[33]. Severance of the extramural pelvic nerves in dogs results in degeneration of the ascending intramural colonic nerve fascicles[34]. Christensen and Schulze-Delrieu have suggested that these ascending nerves of the colon are potentially at risk from mechanical trauma[35]. Analogous to the urinary bladder, changes in colonic motility may be explained by reorganization of efferent pathways following nerve injury. Reinnervation of denervated parasympathetic ganglion cells by sympathetic nerves[36,37] is likely to be important. Interactions between the various pelvic organs is as yet poorly understood but may add to the understanding of some of these motility disturbances[38]. Roe *et al.*[39] were unable to demonstrate differences in motility between a hysterectomized constipated group and another in whom slow transit constipation had occurred *de novo*.

The lack of abnormalities at the sphincteric level is not surprising. The external anal sphincter is innervated by the somatic motor pudendal nerves and is therefore not affected by autonomic nerve damage. In this study the motor innervation of the external anal sphincter appeared functionally intact as assessed by the pudendoanal reflex and supplemented by manometric data. The internal anal sphincter has an extrinsic autonomic innervation but is largely dependent for its function on the intrinsic myenteric plexus which is also responsible for the rectosphincteric reflex[21,34,40,41]. It must be noted, however, that the external urethral sphincter appears to be more susceptible to dysfunction following hysterectomy[6,42].

Resection of the rectum alone can result in motility disturbances of the left colon[43]. It would seem appropriate to treat such patients by left hemicolectomy together with anterior resection of the rectum. In view of the long duration of symptoms in many patients and the resulting laxative abuse, the entire colon may become functionally abnormal due to the long-standing stasis and we prefer to perform a subtotal colectomy with ileorectal anastomosis as for Arbuthnot Lane's disease[44]. The early results appear encouraging. It is conceivable, however, that early detection of this disorder may enable its treatment by less radical surgery or even by pharmacological means, preserving the relatively normal function of the right colon. It must be emphasized that only a small proportion of women undergoing hysterectomy appears to be affected by incapacitating constipation such as that of the group described in this study. Whether this phenomenon is due to technique or to anatomical anomaly remains the subject of further investigation.

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Short note

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Highly selective vagotomy with duodenal dilatation in patients with duodenal ulceration and gastric outlet obstruction

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Since it was described in 1970[1,2], highly selective vagotomy has become an established treatment for duodenal ulceration. Many, however, would regard the presence of gastric outlet obstruction as a contraindication to the procedure[3,4].

Patients and methods

Forty-two patients undergoing surgery between 1973 and 1983 for chronic duodenal ulcer and gastric outlet stenosis under the care of a single consultant surgeon (D.C.D.) are presented All patients underwent highly selective vagotomy combined with duodenal dilatation in 34 and duodenoplasty in eight. The patients formed part of a total experience of 217 highly selective vagotomies performed during this period for duodenal ulcer disease.

In all patients an initial digital assessment of the gastric outlet was performed at operation by attempting to invaginate the gastric and duodenal walls through the lumen of the pylorus. In 50 cases this was not possible and a 2 cm gastrotomy was made in the gastric antrum and the gastric outlet measured using Hegar dilators.

Following the criteria of Kirk for the normal calibre of the gastric outlet[5], obstruction was defined as an outlet measuring <15 mm diameter at operation. In eight patients suspected of having stenosis the outlet was 15 mm or more and the gastrotomy was closed without further action.

The group with stenosis consisted of 31 men and 11 women with an average age of 48 years (range 24–70 years).

The mean duration of ulcer-type pain in the group was 13·2 years (range 6 months to 30 years) and the mean duration of symptoms of gastric outlet obstruction when present was 11·5 months (range 2 weeks to 4 years)

All patients suffered chronic ulcer pain with failure of medical treatment Thirty patients presented the clinical picture of pyloric obstruction with vomiting of food, some with a succussion splash after fasting A further eight patients had radiological evidence of obstruction (large volumes of resting juice, dilated stomach with narrowed outlet or food in the stomach despite fasting) although clinical symptoms were not apparent The remaining four patients were not suspected of having stenosis before operation but had a definite narrowing of the gastric outlet at laparotomy.

In the 42 patients with stenosis, the outlet was narrowed to an average diameter of 10·7 mm (range 3–14 mm) and was dilated by an average of 8·7 mm (range 4–15 mm) to an average diameter of 19·4 mm (range 15–25 mm). Splitting of the duodenum occurred during dilatation in eight This was repaired transversely over a Hegar dilator with interrupted sutures as a single-layer duodenoplasty and an omental patch oversewn.

Insulin testing of vagal integrity on the tenth postoperative day was negative in all cases, suggesting adequate parietal cell denervation A positive response was defined as a basal acid output of >2 mmol/h or an increase of >1 mmol/h following hypoglycaemic stimulation

Each patient was reviewed annually for up to 10 years in a gastric follow-up clinic and assigned a Visick grade by a physician (J O.H) who was not aware whether stenosis had been present.

Results

The average length of hospital stay for the 42 patients was 7·7 days (range 4–22 days). There were no major postoperative complications and no postoperative deaths.

Of the 30 patients with symptomatic stenosis, 27 (90 per cent) had no further trouble with stenosis and 36 of the 42 in the study group (86 per cent) have had no further trouble with duodenal ulceration. Three of the 42 patients (7 per cent) have had clinical and subsequent radiological evidence of recurrent stenosis, two of whom suffered recurrent ulceration and have undergone truncal vagotomy and antrectomy. The third patient developed symptoms of transient gastric outlet obstruction without evidence of recurrent ulceration.

A further four patients have suffered recurrent ulceration alone after 1–6 years on the basis of ulcer-type pain, confirmed endoscopically. Two responded to courses of H_2-receptor antagonists, one remains on long-term treatment and one patient has required a gastrectomy.

One man underwent gastrectomy for carcinoma of the gastric antrum 5 years after highly selective vagotomy.

At their most recent clinic visit, 41 patients (98 per cent) were graded Visick 1 or 2. This includes four patients who underwent further surgery (two for recurrent ulceration with stenosis, one for recurrent ulceration alone and one for gastric carcinoma) and three patients who have required H_2-receptor antagonists for recurrent ulceration. One patient (2 per cent) was graded Visick 3 because of heartburn; biliary reflux was demonstrated on endoscopy.

The incidence of recurrent ulceration in the 175 patients undergoing highly selective vagotomy alone for uncomplicated duodenal ulceration during the same period was 14 per cent.

Discussion

Gastric outlet obstruction occurs in 7–35 per cent of patients with duodenal ulcer disease and is commoner in the Third

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World[4]. The incidence in our series was 19·4 per cent of 217 patients undergoing surgery for chronic duodenal ulcer.

Since it was first described[1,2], highly selective vagotomy has become an accepted operation in the surgical treatment of uncomplicated duodenal ulceration and has repeatedly been shown in prospective randomized trials to be superior to both truncal vagotomy with drainage and selective vagotomy with drainage procedures in terms of postoperative mortality and morbidity and postvagotomy symptoms[6–9].

In the presence of gastric outlet obstruction, the treatment of choice is not clear. In a recent symposium there was unanimous disapproval of the use of highly selective vagotomy in the presence of gastric outlet obstruction because of concern regarding restenosis[3]. Vagotomy with pyloroplasty has been advocated in preference to highly selective vagotomy with dilatation on the basis that the risks of dumping and diarrhoea are preferable to the risk of restenosis[4].

The use of highly selective vagotomy with duodenal dilatation for gastric outlet obstruction from duodenal ulceration was first reported in 15 patients in 1973 by Johnson *et al.*[10]. In 1976 Kennedy reported good results from highly selective vagotomy combined with formal duodenoplasty without dilatation[11]. In 1978 Delaney showed that even tight stenoses could be dilated without fear of restenosis[12] and that, even with long-standing outflow obstruction, gastric tone and emptying will return to normal within 3 months of highly selective vagotomy combined with duodenal dilatation or duodenoplasty[13].

Our rate of recurrent stenosis compares favourably with that of other series that use digital dilatation[14,15], and is comparable with the results of the only other group that has routinely dilated the stenosis up to 20 Fr Hegar[16], i.e. beyond the diameter of the normal outlet[5]. The long-term results also compare favourably with those for alternative procedures[17], particularly in terms of patient acceptability, although we accept the potential pitfalls of comparing our results with historical controls.

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Risk of cancer death in first-degree relatives of patients with hereditary non-polyposis cancer syndrome (Lynch type II): a study of 130 kindreds in the United Kingdom

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To estimate the relative risks of cancer in first-degree relatives of index patients, 130 pedigrees of dominantly inherited Lynch type II cancer family syndrome have been analysed. The risk of death from all causes was significantly increased in women over 45 years of age and the overall liability to cancer in women was greater than for men. A sevenfold increase in risk of colon cancer was found in both sexes. In female relatives the risk of breast cancer was increased fivefold and lifetime risk of breast cancer was 1 in 3·7. A screening programme based on estimated risks could be offered to first-degree relatives of index patients with Lynch type II cancer family syndrome.

Keywords: Hereditary non-polyposis colon cancer, HNPCC, dominant inheritance, relative risks

Family aggregation of colorectal and breast cancer is well recognized by patients and their surgeons and was initially reported by Warthin[1] in 1913. Anderson[2] and Lovett[3] reported an increased risk of colorectal cancer in first-degree relatives of affected men and women, and the risk was particularly high when index patients were young. Anderson[4] and Ottman *et al.*[5] reported an increased risk of breast cancer in first-degree relatives of affected patients that was greater when breast cancer in the index patients was bilateral or affected premenopausal patients. Lovett[3] also reported an increased risk of gastric cancer and breast cancer among first-degree relatives of index patients with colorectal cancer.

Dominant inheritance of a liability to several types of malignancy was reported by Warthin[1] and the importance reinforced by Lynch and Krush[6] in 1971, who revisited Warthin's original family and greatly extended the pedigree. The cancer family syndrome described has been called hereditary non-polyposis colorectal cancer, or Lynch type II syndrome, and extensive kindreds have been reported by Lynch *et al.*[7], usually including colorectal cancers occurring in young adults with a variety of malignancies including breast, pelvic, gastric, skin, brain and bladder. The contribution of hereditary non-polyposis colorectal cancer Lynch type II syndrome to the overall incidence of colon cancer has been estimated as between 6 and 10 per cent by Lynch *et al.*[7], but the risks to relatives of developing specific malignancies has not been estimated.

In Family Cancer Clinics at the Royal Free and St. Mark's Hospitals, London, 999 patients have attended because of their concern about family risks of breast and colorectal cancer. From the pedigrees obtained, those with evidence of dominant inheritance compatible with Lynch type II syndrome have been selected and used to calculate the relative risks of a variety of malignancies, and the lifetime risks have been estimated for first-degree relatives of patients with Lynch type II cancer family syndrome. The findings illustrate the need for surgeons to identify patients belonging to families with a Lynch type II cancer family syndrome and the implications of this diagnosis for the screening of relatives of index patients.

Patients and methods

From 550 patients who have attended St. Mark's Hospital Family Cancer Clinic because of their concern about the family risks of colon cancer and 449 patients who have attended the Royal Free Hospital Genetic Clinic because of their concern about the family risks of breast cancer, 130 pedigrees have been identified with evidence of dominant inheritance of cancers compatible with the Lynch type II cancer family syndrome. Index patients were family members who developed either colon or breast cancer before the age of 50, and all families exhibited a dominant mode of inheritance of two or more different malignancies within the pedigree. Patients attending the clinic were either referred by general practitioners and hospital consultants or presented themselves because of information received from friends, relatives or the media.

The age and cause of death in relatives was verified, where possible, by reference to hospital records or death certificates. Information about living relatives was checked from hospital records. Standard life table methods[8] were used to estimate the years at risk by decades, contributed by male and female first-degree relatives Index patients were excluded from life tables. The median year in which deaths were notified was 1975 and the tables from the Office of Population Censuses and Surveys (OPCS)[9] for 1975 were used to calculate the expected number of deaths among first-degree relatives in 10-year age groups from age 15. The Poisson distribution[10] was used to estimate the significance of any difference between the observed and expected number of deaths. Standard errors obtained from the formula $\sqrt{(\text{observed}^2/\text{expected})}$ for small numbers were used to calculate 95 per cent confidence limits of relative risks; confidence limits were obtained from the table in Breslow and Day[11]

The relative risks of death from all causes, death from all cancers, and death from malignancies recognized to be associated with Lynch type II cancer family syndrome were calculated in three age groups (15–44, 45–64, and 65 and over), and where these were increased the actual risk of death from cancer was calculated.

Results

From 999 index patients attending the Family Cancer Clinics at the Royal Free and St Mark's Hospitals, 130 pedigrees were identified with Lynch type II cancer family syndrome. In all, 99 index patients with breast cancer under the age of 50, and 31 with colon cancer under the age of 50, were identified. Of the first-degree relatives, 885 had reached the age of 15.

Table 1 shows years at risk in three age groups (15–44, 45–64

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and 65 years and over) for both male and female first-degree relatives of index patients with either colon or breast cancer. *Tables 2–5* show the observed number of deaths and relative risks for first-degree relatives for all deaths, all cancers, and cancers of the colon and breast.

Table 2 shows that the expectation of life was diminished in the middle age groups in first-degree relatives of index patients with breast cancers and for the older female relatives of index patients with breast cancer. However, for men, death from all causes was not significantly affected in any age group. *Table 3* shows that there was an increased risk of death from all cancers for both men and women from the age of 45 and that the relative risks for women were between 1·5- and 3·4-fold greater than those for men. *Table 4* shows that both men and women were at increased risk of colon cancer at all ages. *Table 5* shows that the risk of breast cancer was also increased in each age group.

Table 1 *Years at risk contributed by first-degree relatives of index patients with breast cancer and colon cancer by age groups*

Age group of relatives (years)	Index patients with breast cancer		Index patients with colon cancer	
	Female relatives	Male relatives	Female relatives	Male relatives
15–44	10 320	7 395	2950	2390
45–64	3 825	3 075	935	1015
65+	1 260	1 095	332	360
Total	15 405	11 565	4217	3765

The distribution of risks of death from colon, breast and pelvic cancers was similar for first-degree relatives of index patients with breast or colon cancer. It was therefore decided to combine the experience of the relatives of the two groups in considering the risks of rarer malignancies.

Women were also found to be at increased risk of uterine and ovarian cancers, the risk of ovarian cancer being significantly increased, with a relative risk of 3·18. Both men and women were found to be at increased risk of pancreatic and gastric cancer, but for pancreatic cancer only the results for women were statistically significant. The risks for melanoma were significantly elevated for women, but for men the increase

Table 2 *Observed deaths from all causes and the relative risks in first-degree relatives of index patients with breast and colon cancer*

Age group of relatives (years)	Index patients with breast cancer				Index patients with colon cancer			
	Female relatives		Male relatives		Female relatives		Male relatives	
	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk
15–44	8	1·02	10	1·08	16‡	7·37	3	1·0
45–64	39*	1·51	46	1·21	16‡	2·56	15	1·20
65+	73†	1·42	69	0·89	16	0·80	21	0·83
Total	120‡	1·41	125	1·0	48‡	1·93	39	0·95

Significance of difference from expected. *$P<0·05$, †$P<0·01$, ‡$P<0·001$ (Poisson distribution)

Table 3 *Observed deaths from all cancers in first-degree relatives of index patients with breast and colon cancer and their relative risks*

Age group of relatives (years)	Index patients with breast cancer				Index patients with colon cancer			
	Female relatives		Male relatives		Female relatives		Male relatives	
	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk
15–44	5	1·82	1	0·62	14‡	18·67	2	3·77
45–64	30‡	2·71	20†	1·83	16‡	5·97	11‡	3·09
65+	44‡	4·51	37‡	2·14	11‡	3·98	6	1·05
Total	79‡	3·44	58‡	1·95	41‡	6·62	19†	1·94

Significance of difference from expected: †$P<0·01$, ‡$P<0·001$ (Poisson distribution)

Table 4 *Observed deaths from colon cancer and relative risks in first-degree relatives of index patients with breast and colon cancer*

Age group of relatives (years)	Index patients with breast cancer				Index patients with colon cancer			
	Female relatives		Male relatives		Female relatives		Male relatives	
	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk
15–44	1	5·55	0	–	5‡	102·04	1	20·8
45–64	5†	4·15	7‡	6·59	4‡	13·75	4‡	11·53
65+	10‡	5·76	13‡	11·92	4†	7·77	1	1·45
Total	16‡	5·14	20‡	6·06	13‡	15·20	6‡	5·55

Significance of difference from expected: †$P<0·01$, ‡$P<0·001$ (Poisson distribution)

Table 5 *Observed deaths from breast cancer and the relative risks in first-degree relatives of index patients with breast and colon cancer*

Age group of relatives (years)	Relatives of index patients with breast cancer		Relatives of index patients with colon cancer	
	Deaths	Relative risk	Deaths	Relative risk
15–44	2	2·34	2*	8·62
45–64	12†	3·91	3*	4·10
65+	15‡	9·04	4‡	8·71
Total	29‡	5·26	9‡	6·34

Significance of difference from expected: * $P<0·05$, † $P<0·01$, ‡ $P<0·001$ (Poisson distribution)

Table 6 *Living first-degree relatives with cancer by age groups*

Age group of relatives (years)	First degree relatives of all index patients			
	Female		Male	
	Cancer type	*n*	Cancer type	*n*
15–44	Basal cell carcinoma	1	Colon	5
	Melanoma	1		
	Ovary	7 (1 vestigal)		
	Breast	1		
	Colon	2		
45–64	Breast	9	Brain tumour	1
	Breast and ovary	1	Colon	2
	Cervix	3	Skin	1
	Uterus	5	Unspecified	2
	Bladder	1		
65	Breast	10	Bladder	1
	Colon	3	Colon	9
	Melanoma	1	Colon and prostate	1
	Ovary	1	Lung	2
	Sinus	1	Prostate	3
	Uterus	1		
	Basal cell carcinoma	1		
	Skin	1		

was not significant. The risk of lung cancer was increased in women but paradoxically showed a nearly 50 per cent reduction in risk in men. This is consistent with the observations of Lynch *et al.*[7]. The risks of prostate cancer and cancer of lymphatic and haemopoietic tissue were marginally elevated, but the increases were not statistically significant. *Table 6* shows the experience of malignancy in living first-degree relatives by age groups and clearly reflects the increased risk of cancer deaths.

Tables 7 and *8* show a summary of the relative risks and the estimated lifetime risks of death from breast, colon and other malignancies in the first-degree relatives of all index patients in women and in men respectively.

Discussion

Lynch and his co-workers have drawn attention to the increased risk of a variety of malignancies in relatively few large kindreds with cancer family syndrome. In the absence of any diagnostic biomarker it is only from the pedigree that cancer family syndrome can be identified, but the recognition of close relatives of young patients in ordinary surgical practice with colon or breast cancer who may be at high risk of developing a variety of different cancers offers an opportunity for screening a group of people who are anxious and motivated.

Only one first-degree relative under the age of 50 was required to bring patients in our study to the Family Cancer Clinic but two or more relatives affected with a variety of cancers are required to make the diagnosis of Lynch type II syndrome. Since penetration is incomplete, the second cancer in the pedigree is not always in a first-degree relative of the index patient, but dominance can be recognized and the diagnosis can be made if a family history is obtained. Since the analysis was designed to estimate the risks of cancer among first-degree relatives in order to warn surgeons of the need to institute screening programmes for first-degree relatives of young patients with breast and colon cancer, it was decided to include all first-degree relatives of index patients so as to estimate their risks, but to exclude the index patients to overcome ascertainment bias[12].

This analysis of 130 pedigrees allows an estimation of the risks to first-degree relatives of patients with a family history characteristic of Lynch type II syndrome. The risks are relevant not only to a few large kindreds but to a large number of families who recognize an increased liability to cancer among their relatives. *Tables 7* and *8* summarize the findings and show the estimated lifetime risk of death for each type of cancer involved.

There was a notable increase in risk of colon cancer in both sexes which, with melanoma, was disproportionately increased when compared with the overall increase in risk of all cancer deaths and gave a lifetime risk of 1 in 6. For men, the sixfold increase in risk was 1·7 times the expected contribution to all cancer deaths and gave a lifetime risk of 1 in 8. Since most colon cancers arise in a premalignant adenoma, this provides an opportunity for screening and removal of premalignant polyps in an undeniably high-risk group. The fivefold increase in risk of breast cancer in women gave an estimated lifetime risk of 1 in 3·7. Furthermore, the risk was not over by the age of 65 and it may be that screening this high-risk group could successfully reduce mortality as well as morbidity. Cancer of the pancreas and stomach were increased to a lesser extent, and lung cancer

Table 7 *Summary of deaths from cancer in female first-degree relatives of all index patients and all age groups showing observed deaths, relative risks, 95 per cent confidence limits and the lifetime risks*

Cause of death	No. of deaths	Relative risk	95% confidence limits	Lifetime risk
All causes	168*	1·53	1·18–1·61	
All cancers	122*	4·10	3·30–4·71	1 in 1
Colon cancer	29*	7·31	4·70–10·1	1 in 6
Breast cancer	38*	5·18	3·67–7·1	1 in 3·7
Uterine cancer	8†	3·77	1·61–7·37	1 in 40
Ovarian cancer	7†	3·18	0·90–4·66	1 in 20
Pancreatic cancer	7*	5·95	2·32–11·93	1 in 14
Melanoma	4*	10·0	2·71–25·4	1 in 50
Stomach cancer	10*	4·92	2·27–8·68	1 in 14
Lung cancer	6	1·6	0·59–3·49	1 in 17

Significance of difference from expected: * $P<0·001$, † $P<0·01$ (Poisson distribution)

Table 8 *Summary of deaths from cancer in male first-degree relatives of all index patients and all age groups showing observed deaths, relative risks, 95 per cent confidence limits and the lifetime risks*

Cause of death	No. of deaths	Relative risk	95% confidence limits	Lifetime risk
All causes	164*	0·98	0·78–1·1	
All cancers	77*	1·94	1·48–2·34	1 in 1·7
Colon cancer	26*	5·94	3·75–8·45	1 in 8
Pancreatic cancer	3	1·73	0·34–4·94	1 in 50
Melanoma	2	9·9	1·12–35·7	1 in 50
Stomach cancer	10*	1·97	0·82–3·14	1 in 20
Lung cancer	9	0·57	0·26–1·08	1 in 20

Significance of difference from expected: * $P<0·001$ (Poisson distribution) showed a reduction of nearly 50 per cent in men with only a small increase in women.

The predominance of cancer of the colon is entirely compatible with the hypothesis of a major gene exerting a primary influence on the development of colon cancer but increasing the liability to tumour development at other sites in the presence of other genetic or environmental events.

Relative risks of cancer for women were significantly greater than for men; this sex disparity was mirrored in the contribution of cancer to all deaths in female relatives. Although this might in part reflect an increased number of target organs for the development of cancer in women (breast, ovary, uterus), it does not explain the generalized increase in relative risk of cancers of the stomach, pancreas and lung in women compared with men. This observation is consistent with an increased gene penetrance in women. A crude estimate of the degree of penetrance obtained by dividing the difference between observed and expected cancer deaths by the total number of observed deaths due to all causes suggests a penetrance of 27 per cent for men and 78 per cent for women.

The frequency of Lynch type II syndrome may be greater than previously thought and, despite the absence of any biomarker, at-risk individuals may readily be identified by examination of their pedigrees. The quantitative information on relative risks and lifetime risks is now available which could influence clinical practice in terms of designing surveillance and screening programmes for individuals at risk. Such programmes, while focusing principally on monitoring the colonic mucosa, should also address the risk of other neoplasms developing, especially in women. Since the increases are not confined to young age groups, any such strategy adopted should be maintained through the lifetime of the individual at risk.

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Achalasia of the cardia: long-term results of oesophagomyotomy and posterior partial fundoplication

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Forty-eight patients with achalasia of the cardia were treated by Heller's myotomy with a posterior fundoplication of approximately 270°, suturing the gastric fundus to the edges of the myotomy. The mean(s.d.) postoperative follow-up period was 5·4(2·8) years. The clinical results were good to excellent in 44 cases (92 per cent) and fair in four cases (8 per cent) (two with residual dysphagia and two with gastro-oesophageal reflux). Barium studies showed a decrease in oesophageal diameter and disappearance of distal narrowing but normal oesophageal emptying did not occur. Postoperative manometric studies (29 patients) revealed a significant decrease in lower oesophageal sphincter pressure and a significant increase in the length of the infradiaphragmatic segment. In the oesophageal body a recovery of peristaltic waves in the proximal third was seen in ten of the patients (34 per cent). Twenty-four-hour pH monitoring showed pathological reflux in only three of 25 patients studied, and one of these was asymptomatic. This technique is effective, improving oesophageal symptoms and controlling long-term reflux.

Keywords: Oesophageal intraluminal manometry, achalasia of the cardia, Heller's myotomy

Achalasia of the cardia is a disease of unknown aetiology, characterized by loss of peristalsis in the body of the oesophagus and incomplete or absent deglutitive relaxation of the lower oesophageal sphincter which frequently has an increased basal pressure[1–3]. Present treatment aims to suppress the barrier effect of the lower sphincter by dilatation or myotomy.

Since 1977, at the University Hospital of Murcia, achalasia of the cardia has been treated by a Heller's myotomy and an antireflux procedure consisting of a posterior partial fundoplication of approximately 270° and suture of the gastric fundus to the edges of the myotomy. The aim was to create an efficient antireflux mechanism, ensuring that the edges of the myotomy remained separated. Short-term results have been reported[4,5] and Crookes *et al.*[6] published their results in seven patients with a follow-up of 1–3·5 years.

This paper presents the results obtained with this procedure in 48 patients including clinical, radiological and endoscopic assessment and manometric and 24-h continuous oesophageal pH metric evaluation.

Patients and methods

Between 1977 and 1986, 82 patients with achalasia of the cardia were treated surgically Sixty-nine underwent Heller's myotomy with a posterior partial fundoplication. Thirteen patients were excluded as they required other surgical intervention. two patients with previous surgery of the cardia and postoperative gastro-oesophageal reflux with peptic stenosis required resection and coloplasty, in five patients, the Heller's myotomy was associated with an oesophageal longitudinal myotomy by thoracotomy as they presented a vigorous achalasia and six patients required a complete 360° fundoplication to cover accidental perforation of the oesophageal mucosa during operation. Seventeen of the 69 patients with a follow-up of less than 3 years were excluded as well as four who were lost to follow-up.

Forty-eight patients with a mean(s d) age of 44 2(17·4) years (range 13–77 years) were studied There were 27 males and 21 females. Manometric and pH data were compared with a control group of 20 asymptomatic healthy volunteers with normal oesophageal endoscopy and similar age and sex characteristics to the achalasia group (mean(s.d.) age 45(12·8) years, 12 men and eight women). The study protocol was approved by the Human Research Committee of the University Hospital, and informed written consent was obtained from each subject before oesophageal endoscopy and manometry.

The mean(s.d.) time of symptom evolution was 8 1(10 8) years, ranging from 3 months to 45 years. Dysphagia was present in all cases; 40 (83 per cent) had regurgitation, 25 (52 per cent) had thoracic pain and 19 (39 per cent) had weight loss greater than 10 per cent of their body-weight.

Barium studies were obtained in all patients, assessing narrowing of the oesophagogastric junction, presence of tertiary waves and maximum diameter of the oesophageal body, measured in cm. Using Carlson's classification[7], slight dilatation of the oesohageal body (less than 4 cm in diameter) was seen in 17 cases, moderate dilatation (4·1–6 cm in diameter) in 22, and gross dilatation (over 6·1 cm in diameter) in nine.

Preoperative endoscopy allowed the exclusion of organic lesions or associated pathology. A duodenal ulcer was observed in one case only Preoperative manometry confirmed the diagnosis in all patients.

Surgical technique

Through a supraumbilical median laparotomy the abdominal oesophagus and cardia were isolated. Traction was applied on the oesophagus with a ribbon, and a myotomy of 8–10 cm in length was carried out on the anterior distal oesophagus extending for 1 cm towards the gastric wall. The gastric fundus was then mobilized behind the abdominal oesophagus, creating a posterior partial fundoplication of approximately 270° with suture of the stomach to each of the edges of the myotomy (*Figure 1*)

Follow-up

The mean(s.d.) follow-up period was 5 4(2·8) years (range 3–12 years); 19 patients had a follow-up of more than 5 years.

Clinical evaluation

Clinical evaluation was carried out annually on all patients by personal interview and results were considered excellent, good, fair or bad, according to Vantrappen and Hellemans' classification[8] Patients in whom the presence of reflux symptoms required medical treatment were included in the fair group The clinical results were correlated with age (over or under 40 years), sex, period of clinical evolution (more or less than 5 years) and maximum diameter of the oesophagus (<4 cm, 4·1–6 cm and >6·1 cm) Cases with a result considered fair due to the presence of gastro-oesophageal reflux were excluded as this condition was a complication of the surgical technique and did not depend on the mentioned variables.

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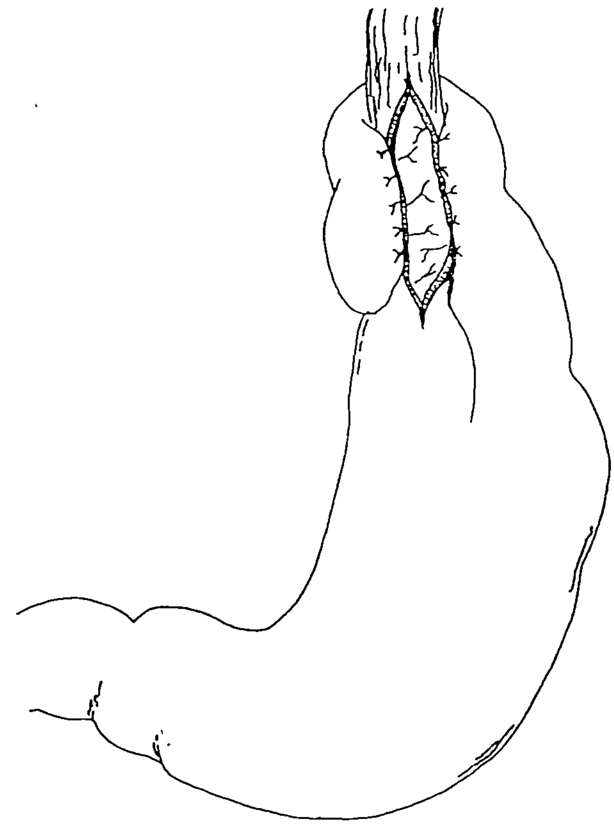

Figure 1 *270° posterior partial fundoplication*

Radiological evaluation

All patients underwent a gastro-oesophageal barium transit study 1 or 2 years after operation.

Endoscopic evaluation

This was carried out every 2 years after surgery to exclude the existence of reflux oesophagitis or the appearance of an oesophageal carcinoma

Manometric evaluation

This was carried out in 29 patients between 1 and 2 years after operation and the results were compared with preoperative values.

pH metric evaluation

Twenty-four-hour pH monitoring was carried out in 25 patients between 3 and 6 years after operation. The results were compared with those of the control group.

Manometric study

To perform oesophageal intraluminal manometry, a 2 m long probe was used with three microtransducers (Gaeltec Ltd., Microtransducers Pressure, Dunvegan, UK). The microtransducers were located at the distal end of the probe, spaced 5 cm apart and oriented circumferentially to lie at 120° to each other. The electric signals of these sensors were picked up by the corresponding amplifiers of a 7754B System polygraph (Hewlett-Packard, Palo Alto, California, USA) and recorded on thermosensitive paper The method has been described before[5] measuring mean basal pressure of the lower oesophageal sphincter expressed in mmHg, total length of the lower sphincter and its infradiaphragmatic length expressed in cm, percentage of sphincter relaxation (considering 100 per cent when the pressure drop reached fundus pressure, it was considered normal when this percentage was greater than 80 per cent), mean basal pressure of the oesophagus (mmHg), mean amplitude of the contractile waves (mmHg), mean duration of these waves (s), mean percentage of tertiary waves, mean percentage of peristaltic waves and mean percentage of spontaneous waves.

pH metric study

A PHM 62·Standard pH meter with a GK 2801 pH electrode (Radiometer A/S, Copenhagen, Denmark) was used, recording on the above-mentioned polygraph which had a direct current amplifier for recording pH (Medium Gain DC Pre-amplifier 8802 A) The method is similar to that described by Johnson and De Meester[9]. Continuous pH recording was performed for 24 h A reflux episode was considered when intraoesophageal pH dropped below 4 The following parameters were evaluated: number of episodes with $pH<4$, number of episodes with $pH<4$ and duration >5 min, total duration of the longest episode (min), total time with $pH<4$ (min) and percentage of total time with $pH<4$

Statistical method

The mean and standard deviation and the median with the quartiles Q1 and Q3 were calculated. For statistical comparison the combined Student's *t*, the paired Student's *t* and the McNemar tests were used according to the groups studied. In some instances, the data were log-transformed and each table specifies where such a transformation has been made and the statistical method used

Results

Operative morbidity and mortality

There were no deaths. Hospital stay averaged 9 days (range 6–22 days). One patient had a left subphrenic abscess which required surgery and three had pneumonia of the left lower lobe. During follow-up, three patients died from conditions unrelated to the oesophageal disease: one from neoplasia of the breast 3 years after operation, one from neoplasia of the gallbladder after 5 years and the third from a cerebrovascular accident 6 years after surgery.

Clinical results

Following the clinical classification of Vantrappen and Hellemans[8], the clinical results were excellent in 33 patients (69 per cent), good in 11 (23 per cent) and fair in four (8 per cent). Two patients were included among the 'fair' for presenting clinical symptoms of gastro-oesophageal reflux. Both were classified as 'excellent' 1 year after operation but developed reflux symptoms at 3 and 6 years. Apart from these two patients there was no other deterioration with time. Two other cases were classified as 'fair' since they had dysphagia more than once a week, especially for solids, although their preoperative situation had improved. The qualification of 11 patients as 'good' was due to the presence of sporadic dysphagia, associated with occasional crises of thoracic pain in three of the 11.

Age, sex, time of evolution of symptoms or oesophageal diameter did not affect the clinical results obtained.

Radiological results

As can be seen in *Table 1*, surgery produced a considerable reduction in the mean(s.d.) maximum diameter of the oesophagus, from 4·9(1·7) cm to 2·7(1) cm ($P<0·001$). A decrease in the incidence of non-propagating waves and the disappearance in 46 out of 48 cases of the distal narrowing of the oesophagus were observed.

Endoscopic results

Oesophagitis was found in three cases, one of them

Table 1 *Radiological results*

	Postoperative ($n=48$)	Preoperative ($n=48$)	*P*
Radiological diameter (cm)			
Mean(s.d.)	2 7(1)	4·9(1·7)	<0·001*
Median (Q1–Q3)	2·7 (1·7–3·5)	4 7 (4–5·5)	
Narrowing of gastro-oesophageal junction (no patients)	2	48	<0 001†
Tertiary waves (no. patients)	4	12	<0 001†

* Paired Student's *t* test; † McNemar test

asymptomatic. Oesophagitis was mild (Savary–Miller grade I)[10] in two cases and severe (Savary–Miller grade III) in the other. In no patient was carcinoma detected.

Manometric results (Tables 2 *and* 3)

A significant decrease in mean(s.d.) lower sphincter pressure was observed (from preoperative values of 22·3(13) mmHg to 15·9(7·2) mmHg) with a significant increase in the length of the infradiaphragmatic portion. No significant modifications were observed in deglutitive behaviour of the sphincter after surgery. The most important changes in the oesophageal body were: a decrease in mean basal pressure, a decrease in the duration of the waves and a decrease in the percentage of tertiary waves. Peristaltic waves appeared in ten of 29 patients (34 per cent) – in seven cases at the proximal third and in three patients throughout the oesophageal body.

pH metric studies (Table 4)

These were carried out in 25 patients and when compared with the 20 controls no significant differences were observed. Three patients, however, showed pathological gastro-oesophageal reflux, with a percentage of time with pH < 4 of 10·7, 13·7 and 23·6 per cent respectively. These were the same three patients with endoscopic oesophagitis.

Table 2 *Manometric results in the lower oesophageal sphincter*

	Postoperative achalasia (n=29)	Preoperative achalasia (n=29)	P*
Mean basal pressure (mmHg)			
Mean(s.d.)	15·9(7·2)	22·3(13)	<0·05
Median (Q1–Q3)	14 (9·5–19·7)	22 (14·1–29·7)	
Total length (cm)			
Mean(s.d.)	3·5(0·68)	3·13(0·5)	n.s.
Median (Q1–Q3)	3·5 (3–4)	3 (3–3·5)	
Infradiaphragmatic length (cm)			
Mean(s.d.)	3·02(0·9)	2·1(0·45)	<0·001
Median (Q1–Q3)	3 (2–4)	2 (1·5–2·5)	
Percentage of relaxation (%) [L]			
Mean(s.d.)	39(33·3)	30·2(31·8)	n.s.
Median (Q1–Q3)	0 (0–68)	0 (0–52)	

* Paired Student's *t* test, [L], log transformation of the data; n.s., not significant

Table 4 *pH metric results*

	Postoperative achalasia (n=25)	Control (n=20)	P*
No. episodes pH < 4			
Mean(s.d.)	11·6(12·6)	13·2(13·7)	n.s.
Median (Q1–Q3)	2 (0–4)	2 (0·5–9)	
No. episodes pH < 4 and duration > 5 min			
Mean(s.d.)	1·8(2·7)	0·4(1·1)	n.s.
Median (Q1–Q3)	0 (0–1)	0 (0–0)	
Duration of longest episode (min)			
Mean(s.d.)	12·6(19·3)	3·4(2·1)	n.s.
Median (Q1–Q3)	2 (0–18)	2 (0–4)	
Total time with pH < 4 (min)			
Mean(s.d.)	31·9(63)	20·8(17·4)	n.s
Median (Q1–Q3)	3·5 (0–30)	4·5 (1–8)	
Percentage of time with pH < 4			
Mean(s.d.)	1·6(3·9)	1·6(1·1)	n.s.
Median (Q1–Q3)	0·2 (0–2)	0·3 (0·1–0·5)	

* Combined Student's *t* test; n.s., not significant

Discussion

Treatment for achalasia of the cardia remains controversial. Some[8,11] maintain that initial treatment should be conservative, reserving surgery for failure, and others[1–5,12–20] favour surgery as the initial treatment, reserving dilatation for when surgery is not successful.

Surgical treatment has the following advantages: little or no morbidity or mortality[1–3,12,21], immediate excellent or good results in over 80 per cent of the patients[2,12,13,21,22] which do not deteriorate with time[2,12,21,22], it can be used in children and psychotic patients[21,23], it is effective in wide oesophageal dilatations although results are not so good[1,21,24], and other pathology may be recognized and treated[1,22]. The choice between surgery and dilatation may depend upon the quality and experience of surgeons and endoscopists in each institution.

Some have published excellent results with isolated myotomies[2–14], without an antireflux procedure and stressing that the myotomy must be short (extended < 1 cm to the stomach) and surgically respect the structures which hold the oesophagus passing through the diaphragm. Myotomy alone causes a decrease in lower oesophageal sphincter pressure, but

Table 3 *Manometric results in the oesophageal body*

	Postoperative achalasia (n=29)	Preoperative achalasia (n=29)	P*
Mean basal pressure (mmHg)			
Mean(s.d.)	−4·8(3·1)	−0·14(5·7)	<0·001
Median (Q1–Q3)	−5·5 ([−6·5]–[−2·75])	−1 ([−5]–[−3·75])	
Mean wave amplitude (mmHg)			
Mean(s.d.)	15·7(14)	19·1(18·6)	n.s.
Median (Q1–Q3)	13 (8·7–20·8)	17·3 (9·8–22·2)	
Mean wave duration (s)			
Mean(s.d.)	3·5(1·18)	4·9(1·6)	<0·01
Median (Q1–Q3	3·45(2·5–3·9)	5·5(3·7–4·8)	
Percentage of tertiary waves [L]			
Mean(s.d.)	83·7(25·8)	100(0)	<0·001
Median (Q1–Q3)	83·3 (66·7–100)	100 (100–100)	
Percentage of peristaltic waves [L]			
Mean(s.d.)	16·4(26·2)	0(0)	<0·01
Median (Q1–Q3)	0 (0–33·3)	0 (0–0)	
Percentage of spontaneous waves [L]			
Mean(s.d.)	0(0)	2·6(8·4)	n.s.
Median (Q1–Q3)	0 (0–0)	0 (0–0)	

* Paired Student's *t* test, [L], log transformation of the data, n.s., not significant

the sphincter remains with a sufficient resting pressure to prevent gastro-oesophageal reflux, which responds with pressure increments to increases in abdominal pressure[25]. Postoperative gastro-oesophageal reflux in a patient with an aperistaltic oesophagus is the main drawback of this method, as shown by studies which assess long-term reflux[26,27] using techniques such as 24-h continuous oesophageal pH monitoring[28].

The technique described here decreases the tone of the lower oesophageal sphincter but adds an antireflux procedure[2,3,15–20], attempting to create a high pressure zone with a length and basal tone similar to normal.

Excellent to good results were obtained in 92 per cent of our patients after a follow-up period of 5·4 years and these data compare favourably with those of other series[2,3,12,29]. Results do not correlate with age, sex, duration of symptoms or degree of oesophageal dilatation – as reported by Ellis *et al.*[12] but contrary to others[21].

The radiology results are similar to those described by others[2,23,29] and, despite improvement, oesophageal emptying is slowed, as shown in isotope studies[30]. The myotomy suppresses the barrier effect of the lower sphincter but does not allow recovery of normal peristalsis in the oesophageal body.

The manometric results show that sphincter pressure decreases, but leaves an area of high pressure with a sufficient basal tone. A significant increase is observed in its infradiaphragmatic segment, which is important for ensuring the absence of gastro-oesophageal reflux.

In the oesophageal body there was a decrease in mean basal pressure, tending to normality, as has been reported by others[2,3,29]. One interesting observation was the appearance in some patients of peristaltic waves, basically restricted to the upper half of the oesophagus but in some cases (three out of ten) observed throughout the oesophageal body. This postoperative manometric observation noted by others[2,3,30] suggests that achalasia forms part of a wide spectrum of primary oesophageal motor disorders[31,32].

Oesophagomyotomy and posterior partial fundoplication is a procedure which allows correction of many physiological and anatomical abnormalities in achalasia of the cardia.

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Intersecting staple lines and blood flow in oesophagojejunal anastomoses

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Total gastrectomy and oesophagojejunostomy with linear stapling devices were performed on 22 pigs to evaluate whether intersecting staple lines reduce the blood flow with an increased risk of anastomotic leakage. The blood flow at intersecting staple lines and single row staple lines of the anastomosis was studied with the reference organ method 24 h after the first operation. The mean blood flow in intersecting staple lines was 0·305 ml min^{-1} g^{-1} tissue and 0·307 ml min^{-1} g^{-1} tissue for single row staple lines. The confidence interval for the reduction in blood flow for intersecting staple lines compared with non-crossing staple lines was from −16 to +17 per cent. In one animal the reduction in blood flow was 37 per cent; in all other animals there was no reduction in blood flow or a reduction less than 25 per cent. An equivalence test shows that if a reduction in blood flow exists it is most likely to be less than 30 per cent (P<0·001). Our data confirm that intersecting staple lines in oesophagojejunal anastomoses do not reduce mean anastomotic blood flow to a dangerous level.

Keywords: Oesophagojejunal anastomosis, stapling devices, microcirculation, total gastrectomy

Since the introduction of the EEA® stapler by the US Surgical Corporation (Norwalk, Connecticut, USA) in 1967, stapling has gained widespread popularity in gastrointestinal surgery[1]. This is particularly true for oesophageal, gastric and colorectal surgery[2–5]. Numerous surgeons report excellent results with the EEA stapler when performing oesophagojejunostomy after total gastrectomy[2,3,6,7]. In a prospective study of anastomotic failure following total gastrectomy, Viste and co-workers showed that the risk for anastomotic leakage was 2·4 times greater for hand-sutured anastomoses than stapled anastomoses[8].

In spite of the good results reported there are problems associated with circular stapling devices in oesophageal surgery[9,10]. If the oesophagus is narrow it can be damaged or even ruptured when the anvil is introduced into it. There are methods to dilate the oesophagus or to facilitate the introduction of the stapler[11,12]. Anastomosis with the circular stapler demands a purse-string suture. This suture is often time consuming and the purse-string instrument is reported to be associated with cases of intraoperative failure[9]. When performing oesophagojejunostomy with the double stapling method described previously by the authors[10] there is no need for a purse-string suture and, furthermore, the width of the oesophagus is not a contributing factor (*Figure 1*).

Because many operations for gastric carcinoma are palliative and local recurrence is the most common site for recurrent disease, it is important to have a wide anastomosis[13] The width of the oesophagojejunostomy performed with the double stapling method is either equal to or greater than that achieved with the EEA stapler when measured 6 months after operation[10]. The double stapled anastomosis is performed side-to-side with the PLC 50® (Ethicon Ltd., Somerville, New Jersey, USA) or GIA® (US Surgical Corporation) device, and when the residual opening is closed with the RL 60® (Ethicon Ltd.) or TA 55® (US Surgical Corporation) device the previous staple lines of the PLC 50 or GIA are crossed (*Figure 1*). The only leak reported by Walther and co-workers[10] in a clinical series using this anastomosis was in the corner of the intersecting staple lines, and ischaemia was suspected (*Figure 1*). So far no study has evaluated the blood flow in crossing staple lines, although Chung *et al.*[14], who studied the effect of stapling on blood flow in colonic anastomoses, showed that tight stapling gave a considerable decrease in suture line blood flow.

If intersecting staple lines lead to increased damage to suture line tissue with a reduction in the circulation to parts of the anastomosis it would constitute a hazard in the anastomosis with an increased risk of anastomotic leakage and patient morbidity and mortality. Haglund *et al.*[15] have shown that the

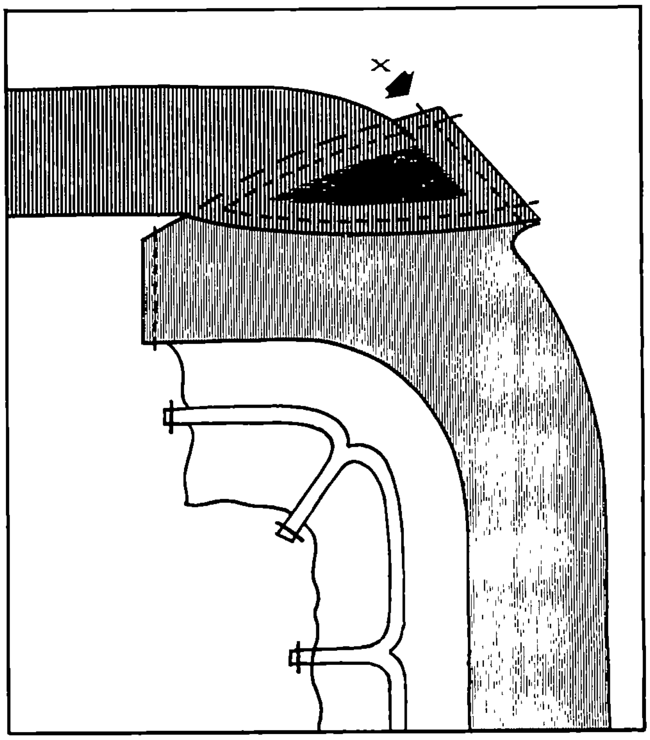

Figure 1 *Oesophagojejunostomy performed with two linear stapling devices. The only leak in the series by Walther and co-workers*[10] *occurred at the point marked X*

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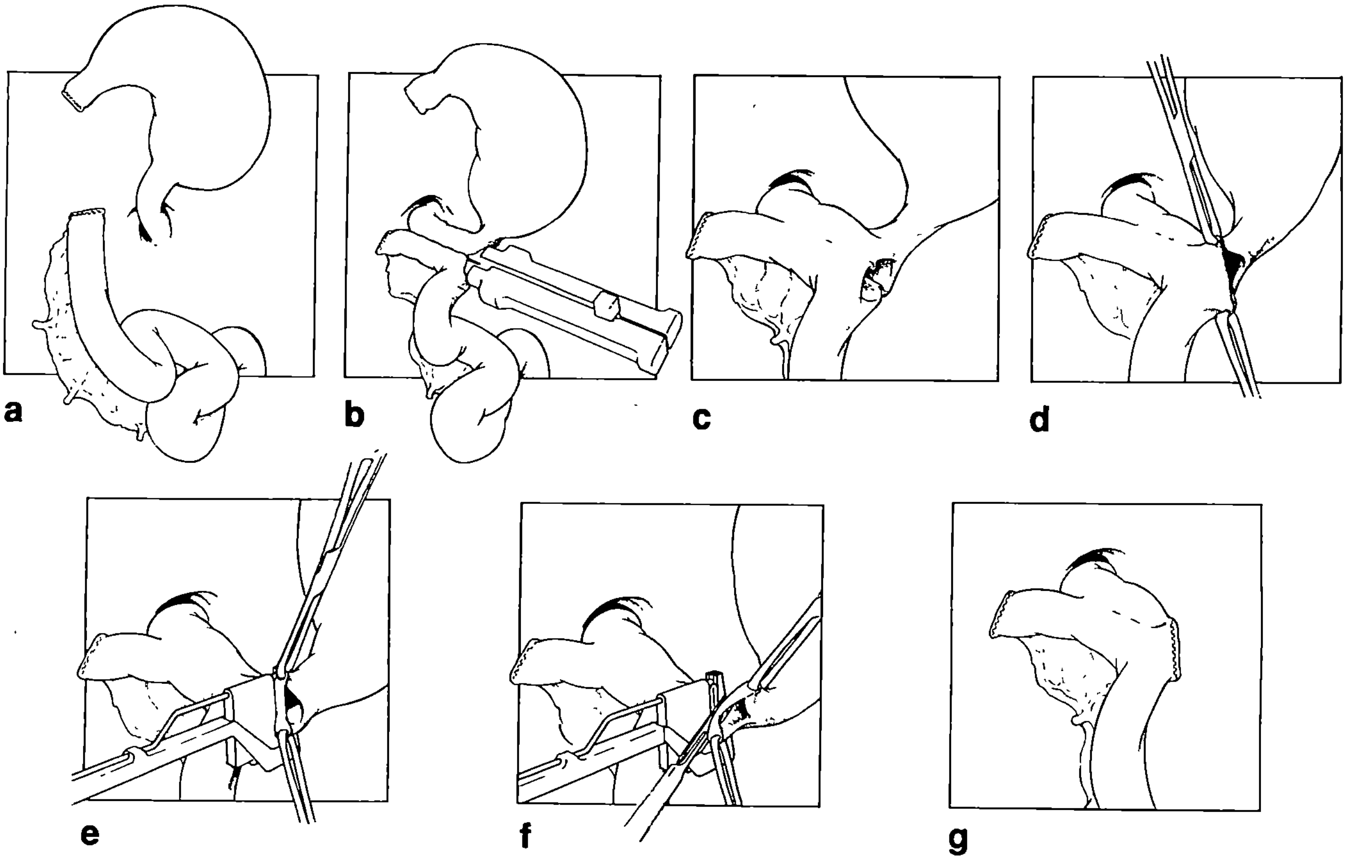

Figure 2 *End-to-side oesophagojejunal anastomosis with linear stapling devices after total gastrectomy.* (**a**) *The jejunum is divided with the PLC 50 device and a Roux-Y loop is prepared, the stomach, attached only to the oesophagus, is placed on the pig's chest,* (**b**) *the oesophagus and Roux-en-Y loop are brought together and the instrument is closed and fired,* (**c–d**) *the instrument is withdrawn and the ends of the two staple lines are held by Allis clamps and moved laterally,* (**e–f**) *the residual opening is closed with an RL 60 stapler;* (**f–g**) *surplus tissue is cut and delivered with the specimen*

mucosa, the most vulnerable part of the intestinal wall, can stand a 30 per cent reduction of blood flow without infarction.

This study evaluates in an animal model whether intersecting staple lines reduce staple line blood flow to a dangerous level in oesophagojejunal anastomoses performed with linear stapling devices.

Material and methods

Animals

Twenty-two standard Swedish domestic pigs underwent operation Fourteen pigs were male and eight were female, with an average weight of 20·1 kg (range 14·5–27·0 kg). Twenty-four hours before operation, food was withdrawn. The pigs were anaesthetized with pentobarbital and an endotracheal intubation was performed. The animals were artificially ventilated with nitrous oxide and oxygen One litre of Ringer–glucose solution was given during the operation.

Surgical procedures

All operations were performed by the same surgeon under sterile conditions. Through a midline incision the stomach was mobilized from the greater and lesser omenta The left and right gastric arteries, the gastroepiploic artery and the short gastric vessels were ligated and divided. When the stomach was attached only to the oesophagus and the duodenal bulb, the latter structure was divided with the PLC 50 The stomach, now attached only to the oesophagus, was then placed on the chest (*Figure 2a*). Twenty centimetres below the ligament of Treitz the jejunum was divided with the PLC 50 device and a Roux-en-Y loop with a length of 40 cm was prepared (*Figure 2a*). One incision was made into the back wall of the oesophagus and one was made antimesenterically on the Roux-en-Y loop 5 cm distal to its closed end The oesophagus and the Roux-en-Y loop were brought together and the instrument was closed and fired. After withdrawal of the instrument, the ends of the two staple lines were held by Allis clamps and moved laterally. The residual opening was closed with a RL 60 stapler. The surplus tissue was cut and delivered with the specimen An enteroanastomosis was performed 40 cm distal to the oesophagojejunostomy, and the abdomen was closed.

Measurement of blood flow in the anastomosis

The blood flow at different sites at the anastomosis was measured 24 h after the first operation with the reference organ method according to Bartrum *et al.*[16]. The pigs were anaesthetized for a second time The left femoral artery was exposed and connected to a syringe in a withdrawal pump Through a thoracotomy, 75×10^6 ^{57}Co-labelled microspheres (NEN-TRAC®, Du Pont Scandinavia AB, Stockholm, Sweden) were injected into the left ventricle of the heart. For 2 min after the cardiac injection of microspheres, blood was drawn from the left femoral artery into the syringe (the reference organ) at a flow rate of 0·6 ml min^{-1}. The animals were killed by an intracardiac injection of Mebumal® (Nordvacc AB, Stockholm, Sweden)

Samples were taken from the left and right kidneys to evaluate the mixing of blood and spheres. The oesophagojejunostomy was opened on the opposite side of the everted suture line and samples (4 × 4 mm) were cut with a two-bladed cutter from the oesophageal and jejunal side of the intersected staple lines As there were two corners of intesecting staple lines in each anastomosis, four samples were taken from intersecting staple lines on each pig. Another two samples of the same size were cut on either side of the everted suture line (*Figure 3*). The activity of the samples was measured in a high pure germanium-detector consisting of a Canberra one open end coaxial germanium detector, a Canberra spectroscopy amplifier model 2020 (Canberra Industries Incorporated, Connecticut, USA) and a Nuclear Data ND 66 multichannel analyser (Nuclear Data Incorporated, Schaumburg, Illinois, USA)

The arterial blood flow, f_i (ml min^{-1}), in an organ (i) can be calculated using the equation:

$$f_i = (q_i/q_r) f_r$$

where f_r is the known blood flow in the reference organ (r) and q_i and q_r are the amounts of radioactivity (Bq) in the organ i and in the reference organ r, respectively. Use of this formula requires that the microspheres have been well mixed with blood before leaving the heart. Assuming that the organ under study is uniformly vascularized, specific organ

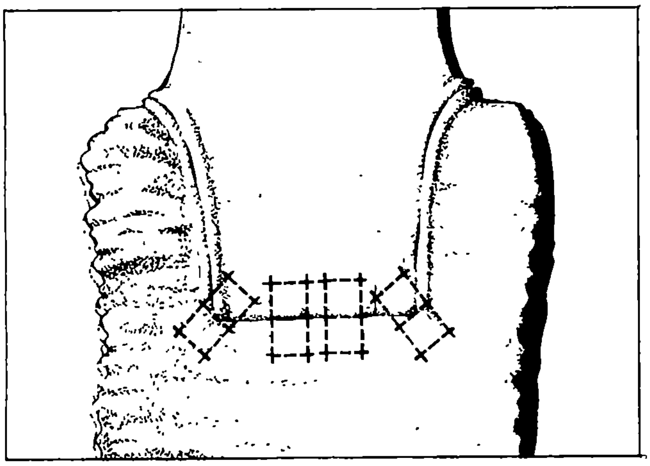

Figure 3 *From the oesophagojejunostomy 4 × 4 mm samples of the entire wall were taken on each side of the crossed staple lines and from both sides of the everted staple line for measurement of the anastomotic blood flow*

blood flow can be calculated from measurements of activity in an organ sample·

$$f_i/m_i = f_i \text{ sample}/m_i \text{ sample} = (q_i \text{ sample}/q_r) \times (f_r/m_i \text{ sample})$$

where m_i denotes the weight of the organ i.

Statistical methods

A paired Student's *t* test was used to compare the blood flow in intersecting and non-intersecting staple lines. A paired one-sided equivalence test was used to investigate whether the mean blood flow was reduced by 30 per cent or more (0·10 ml min^{-1} g^{-1} tissue) for intersected suture line parts. Statistical procedures for such tests have been reviewed by Com-Nougue and Rodary[17]. A *P* value of 0·05 or less was considered to be statistically significant The sample size was calculated to achieve 5 per cent significance and 80 per cent power.

Results

Seven pigs died after operation. The autopsy showed one anastomotic failure in the cranial part of the anastomosis. In a second pig, by mistake, only the oesophageal musculature had been incised leaving the mucosa complete. In this pig the PLC 50 stapler was introduced in the layer between the muscular layer and submucosa of the oesophagus and the result was non-patency of the anastomosis between the oesophagus and the bowel. In the third pig the closure of the RL 60 became too tight leaving no space in the anastomosis. The remaining four pigs had watertight anastomoses and died from anaesthetic complications.

The specific kidney blood flow was calculated for each animal. The correlation coefficient between left and right kidney was 0·93, indicating good distribution of the microspheres within the blood.

Anastomotic blood flow

The median number of microspheres per sample was 358 (range 14–3988) in samples from intersecting staple lines and 345 (18–1428) in samples from non-intersecting staple lines. *Table 1* gives the blood flow for crossing and non-crossing staple lines, and the histogram in *Figure 4* shows the distribution of blood flow reduction for samples from crossing staple lines. The 95 per cent confidence intervals for the reduction in blood flow for intersecting staple lines compared with non-crossing staple lines were from −16 to 17 per cent.

In one animal the reduction in mean blood flow was 37 per cent; in all other animals there was no reduction in mean blood flow or a reduction less than 25 per cent.

The blood flow was slightly, but not significantly, higher in intersecting sites than in single row sites ($P = 0·944$). The equivalence test indicated that the mean blood flow in intersecting sites was significantly higher ($P < 0·001$) than that implied by a 30 per cent reduction.

Discussion

Oesophagojejunostomy with linear stapling devices has many advantages over oesophagojejunostomy with circular staplers. With linear stapling devices there is no risk of oesophageal rupture as has been described with the EEA stapler in the case of a narrow oesophagus[9]. There is no need for the time-consuming purse-string suture to be performed and, finally, the anastomotic diameter is either greater than or equal to that of an EEA-stapled anastomosis[10].

We have, in a previously reported series of 15 patients, performed oesophagojejunostomy after total gastrectomy with linear stapling devices[10]. There was one leak after operation This leak arose in the corner of the intersecting staple lines; whether it was due to technical failure or ischaemia could not be determined at reoperation[10]. This case gave impetus to the present study.

Ravitch *et al.*[18] have studied the validity and safety of stapled functional end-to-end intestinal anastomoses in dogs with either a perforation or an obstruction in the midcolon. In 35 dogs they noted six leaks where the GIA staple line crossed the TA 55 staple line. In undamaged bowel, however, Ravitch[19] claims that intersecting staple lines are just as safe as non-crossing staple lines. Whether anastomotic blood flow is reduced at the sites of intersecting staple lines has not yet been studied. Studies evaluating oesophageal anastomotic circulation are extremely few, and are non-existent with regard to crossing staple lines.

There are several techniques to measure organ blood flow. Zierler presented the fundamentals for organ blood flow measurement in 1962[20]. Lassen and Ingvar[21] and Darle[22] further improved the technique by introducing radiolabelled indicators, while Bartrum *et al.*[16] described the reference organ method used in this study in 1974. Chung[14] has studied blood flow in colonic anastomoses with a laser Doppler technique in an acute experiment using the microsphere technique to

Table 1 *Blood flow in oesophagojejunal anastomoses (ml min^{-1} g^{-1} tissue)*

	Mean	s.d	s.e.m.
Crossing staple line ($n = 60$)	0·305	0·29	0·037
Non-crossing staple line ($n = 60$)	0·307	0·29	0·037

n.s , Not significant

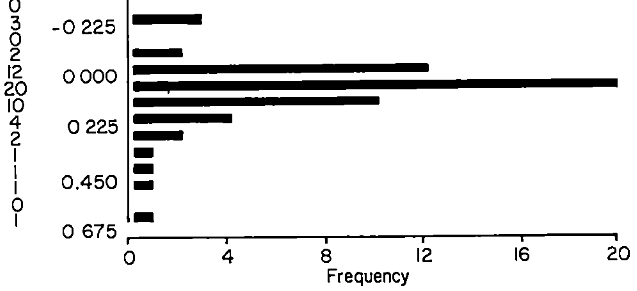

Figure 4 *Distribution of reduction in blood flow per sample(ml min^{-1} g^{-1} tissue)*

evaluate the laser Doppler measurements. There was good agreement between the two methods, and Chung found a 43 per cent reduction in mucosal blood flow in stapled anastomoses with the staple closure height equal to the thickness of the two bowel walls. If the staple closure was set to half of the combined wall thickness, suture line blood flow was reduced by 69 per cent[14].

These results are quite the opposite of those of Graffner and co-workers[23] who used the microsphere technique and found a higher blood flow at the anastomotic site compared with sites located 80 mm proximally and distally. The contradictory results may be due to the fact that with the microsphere technique all bowel layers are included in the measurement while the laser Doppler technique is limited by the penetration depth of the flow probe. In Chung's study the probe was limited to a penetration depth of 1 mm, making it impossible to study layers deeper than the mucosal circulation

The most plausible explanation for hyperaemia in the experiment by Graffner *et al.*[23] is, however, the fact that the animals were killed after 1 week. The higher blood flow seen at the time probably reflects the inflammation and proliferation of the healing phase. Walther *et al.*[24] have previously studied anastomotic blood flow in oesophagojejunal anastomoses with the reference organ method and also found anastomotic hyperaemia in the oesohagojejunostomy compared with a site 100 mm proximal to the anastomosis. These measurements were also done 1 week after operation.

In the present study no reduction in blood flow was found at the site of intersecting staple lines 24 h after operation. It can be assumed that the four samples from crossing and non-crossing sites at the anastomoses are independent of each other (*Figure 3*). The equivalence test indicated that, if a reduction exists, it is most likely to be less than 30 per cent

The extent to which anastomotic blood flow can be reduced without causing anastomotic breakdown is not known. Studies by Haglund *et al.*[5] have shown that a reduction of the intestinal blood flow of 30–50 per cent leads to mucosal infarction in cats. The mucosa is the most vulnerable part of the gut. These observations suggest that the anastomosis will survive a flow reduction of up to 30 per cent without danger of breakdown.

The sources of error with the microsphere technique used by us are of two kinds, technical and biological. The technical errors include misread observations, calibration errors and incorrect weighing of test tubes. Biological errors consist of irregularities in the distribution of microspheres to the vascular bed. According to Buckberg *et al.*[25] the ideal number of microspheres per sample is 400. With a smaller number the statistical error becomes too large, while a much greater number will lead to blockage of parts of the vascular bed. With our median values of 358 and 345 microspheres respectively per sample, we believe that we are close to the ideal number of microspheres.

In conclusion, our data confirm that intersecting staple lines in oesophagojejunal anastomoses do not reduce anastomotic blood flow to a dangerous level. They also indicate that the statement by Ravitch *et al.*[18] that intersecting staple lines are secure in intestinal anastomoses is valid for oesophageal anastomoses.

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Surgical results of intrathoracic gastric volvulus complicating hiatal hernia

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From 1981 to 1988, 138 patients with hiatal hernia were treated surgically at our centre. Twenty-one (mean age 76·6 years, 17 women, four men) had an associated intrathoracic gastric volvulus. Eleven patients (mean age 73·2 years), of whom eight were asymptomatic, had an elective procedure. Ten patients (mean age 80·3 years) had emergency surgery, six for acute complications of the volvulus (five cases of strangulation and one of perforated ulcer) and four because of other, unrelated causes of acute abdomen. There were four deaths after operation, all in the emergency surgery group. Four other patients had significant morbidity, all in the emergency group. In the elective cases, all hernias were easily reduced. In one emergency case a gastrotomy was necessary for decompression, and in another gastrectomy was necessary because of gastric gangrene. Our results indicate the need for elective intervention when intrathoracic gastric volvulus is first diagnosed.

Keywords: Gastric volvulus, hiatal hernia

Intrathoracic gastric volvulus is a rare complication of hiatal hernia. It is caused by gastric torsion around one of the axes after a partial or complete passage of the stomach through the hiatal orifice. It complicates 5–10 per cent of hiatal hernias reported in the literature[1,2]. It represents the ultimate stage of a rolling hiatal hernia and is evidence of the failure of gastric fixation structures, explaining its occurrence in the elderly[1,3]. This is in contrast to intrathoracic gastric volvulus associated with traumatic or diaphragmatic defects or hernias[4].

The risks of elective surgical intervention in an elderly population must be weighed against the risks of complications if intrathoracic gastric volvulus is left untreated. We review here our experience with surgery for intrathoracic gastric volvulus.

Patients and methods

From 1981 to 1988, 138 patients with hiatal hernia, 117 sliding or mixed hernias without volvulus and 21 with intrathoracic gastric volvulus, were treated surgically. The 21 cases of intrathoracic gastric volvulus form the basis of this analysis of operative mortality and morbidity risk.

Of the 21 patients, 17 were women and four were men, with a mean(s.d.) age of 76·6(7·7) years. Prior medical histories included five patients with angina, seven with hypertension, three with cardiac failure, one with rheumatoid arthritis, one with poliomyelitis, two with previous carcinomas (anal canal, renal), two with previous cholecystectomy and three who had undergone total hip replacement. At the time of treatment for intrathoracic gastric volvulus, nine patients had had a hiatal hernia diagnosed for a mean of 15 years (range 3–30 years). Eleven patients had an elective procedure (mean(s.d.) age 73·2(8·1) years) and ten had emergency surgery (mean(s.d.) age 80·3(4·5) years).

Results

Of the ten emergency cases, six operations were undertaken for acute complications of intrathoracic gastric volvulus (mean(s.d.) age 84(3·4) years). Of the six volvulus complications, five were cases of strangulation and one was a perforated gastric collar ulcer. Overall, eight patients with intrathoracic gastric volvulus were asymptomatic and 13 had various symptoms such as atypical gastric pain ($n=3$), fever ($n=3$), pseudoangina ($n=3$), obstructive episodes ($n=3$) and anaemia ($n=7$), of whom five patients required transfusion).

The five patients with strangulated volvulus had severe epigastric pain and inability to retain food, which was associated with haematemesis in two cases. The patient with the perforated gastric ulcer presented with typical signs and symptoms of a perforated hollow viscus.

Four patients with a history of acute abdominal complaints (two duodenal ulcer perforations, one intestinal obstruction by cancer of the right colon, one obstruction by strangulated femoral hernia) underwent reduction of their volvulus at the same time.

Chest radiography in all cases showed a clear retrocardiac image with disappearance of the gastric air bubble. In the 11 elective cases, barium studies confirmed the presence of the stomach within the thorax. In three cases, there was an associated sliding hernia. In four of the five cases of strangulated volvulus, Gastrografin (Schering) swallow showed complete blockage, one at the level of the lower oesophagus, another at the greater curve and two at the pylorus. In the fifth case, a barium swallow was not performed because of the suspicion of pneumoperitoneum on abdominal plain film.

Endoscopy was attempted in six of the seven anaemic patients and showed oesophageal ulcers in four and nothing specific in two cases. A barium enema performed in two cases showed an intrathoracic transverse colon in one.

Treatment

Treatment was surgical in all cases. In all five strangulated cases there had been an unsuccessful attempt at reduction by nasogastric suction.

The surgical approach was abdominal in all cases. The stomach was seen to be pushed into the thorax with the pylorus at the oesophageal hiatus. The transverse colon was partially herniated in three cases. In emergency cases, the volvulus was complete in seven patients and incomplete in three. Whether the volvulus was of organoaxial or mesentericoaxial character was not noted. In elective cases, the volvulus was complete in seven cases and incomplete in four.

In the elective surgical cases, reduction of the herniated stomach was always easily accomplished by gentle gastric

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traction. In one case of strangulated volvulus, it was first necessary to decompress the stomach by a short gastrotomy before reduction. In four of five strangulated cases, the gastric wall regained normal colour after reduction, but in one case the stomach and transverse colon were gangrenous, necessitating total gastrectomy and transverse colectomy without re-establishing continuity.

The hiatal orifice was always large, estimated to be at least 10 cm in diameter. The diaphragmatic pillars were always found. In one case, the aorta and oesophagus had a common orifice. Resection of the hernia sac was total in 19 cases and partial in one case. In the remaining case resection was judged to be too dangerous after portal hypertension was discovered at surgery.

The hiatal orifice was narrowed in all cases by approximation of the pillars in front of and behind the oesophagus by several non-absorbable sutures, so that the oesophageal orifice admitted one finger. An antireflux procedure was performed in all cases In ten patients a Nissen procedure was undertaken In three patients posterior or anterior valves were created by fixing the gastric fundus to the right of the oesophagus with non-absorbable sutures, the fundus having been passed posteriorly to the oesophagus when forming a posterior valve or anteriorly when creating an anterior valve. In seven patients the gastric fundus was sutured to the left side of the oesophagus with non-absorbable sutures.

In seven of the 11 elective cases, a second procedure was also performed. One patient had an inferior oesophageal myotomy because of an epiphrenic diverticulum, a splanchnicectomy because of operative diagnosis of pancreatic carcinoma with peritoneal carcinomatosis, a portocaval anastomosis for portal hypertension, repair of a strangulated femoral hernia, and a subtotal thyroidectomy for associated hyperthyroidism. Two patients also underwent cholecystectomy.

Pyloroplasty was performed in three cases, in two because a truncal vagotomy had been needed to free the oesophagus and in the third because of an associated perforated duodenal ulcer.

During surgery, one patient suffered an extramucosal oesophageal injury; this was treated by direct suture and a Nissen procedure, and caused no complications. In one case, resection of the hernia sac was complicated by a left pleural tear.

Outcome

There were four deaths after operation, all in emergency surgical cases, giving a mortality rate of 19 per cent overall and of 40 per cent for emergency cases. Three deaths (one due to multiple system failure and two to aspiration pneumonitis) occurred in the five patients with an isolated strangulated volvulus, giving a 60 per cent mortality rate in cases of complicated volvulus; another patient died from aspiration pneumonitis following repair of a strangulated femoral hernia with associated intrathoracic gastric volvulus The mean(s.d.) age of patients who died was 77·2(3·4) years

Postoperative morbidity was encountered in four of the 21 cases (19 per cent) and was due to respiratory failure, pulmonary embolism, air embolus due to accidental disconnection of a central line, and wound infection. All these patients were in the emergency group (40 per cent morbidity of emergency cases), two because of strangulated volvulus and two because of other causes of acute abdomen.

The mean(s.d.) hospital stay was 11·4(6) days and was identical for patients having elective or emergency surgery.

Of the surviving 17 patients, four were lost to follow-up and one died at 3 months from pancreatic cancer found at operation. Twelve patients have been followed for a mean of 9 months (range 2–24 months). Of these, ten have had excellent results, another had a fair result with episodes of dysphagia due to a tight hiatal ring confirmed by barium study at 9 months, and the last patient had a poor result due to the recurrence of gastro-oesophageal reflux (with oesophagitis on endoscopy) 5 months after operation.

Discussion

The 15 per cent frequency of intrathoracic gastric volvulus complicating hiatal hernia seen during a 7-year period at our centre is comparable with the frequency cited in the literature[1,2], as is the preponderance of women and the advanced age at diagnosis[1]. We did not encounter any familial cases[5].

The variable signs and symptoms of intrathoracic gastric volvulus, as well as the large proportion of asymptomatic patients (eight of 21 in our series), explains why the diagnosis is often made late and at advanced age[1,2,6] on routine chest radiography or when complications ensue. Gastro-oesophagal reflux may give rise to epigastric pains which typically are intermittent during periods of engorgement or associated with problems of gastric emptying[7]. Iron deficiency anaemia or upper gastrointestinal haemorrhage may be due to oesophagitis following reflux, gastric ulceration due to localized ischaemia and acidity held within the herniated stomach by the abdominothoracic pressure gradient, or mucosal congestion due to venous obstruction of the herniated stomach[1]. The transverse colon may also herniate[8]. A pseudoanginal syndrome with pains suggesting angina pectoris and sometimes associated with electrocardiographic changes may make for a difficult differential diagnosis in the elderly[9]. More rarely, obstructive jaundice may occur if the pylorus is pulled up to the level of the hiatus compressing the common bile duct[10]. Complications, which may be the first sign of intrathoracic gastric volvulus[11], include strangulation causing severe epigastric pain and postprandial vomiting or, more rarely, perforation of a gastric ulcer[12].

The presence of intrathoracic gastric volvulus should be suspected if routine chest radiography shows a clear retrocardiac image, and the diagnosis may be confirmed by barium studies. Endoscopy is generally indicated only if the cause of iron deficiency anaemia is being sought[1]. The facts that volvulus is found in older patients and that the associated clinical symptoms are mild explain why a relatively large number of patients undergoing surgery have had complications[2,6,13]. Our series shows that the only factor influencing mortality was the need for surgery to deal with such complications of volvulus. Because the development of complications is totally unpredictable, our results suggest that surgery is indicated when the diagnosis of volvulus is made, regardless of the patient's age.

In our series, and in most others, the surgical approach used was abdominal[13], although others have preferred a thoracic approach[1,4] in the three following situations:

1. When the volvulus is strangulated or return of the stomach to the abdomen is difficult. In our hands it was always possible to reduce the volvulus by emptying the gastric contents.
2. In cases of repeated earlier engorgements, intrathoracic adhesions may be formed[13] although this was not seen in our series.
3. In the case of an associated stenosed oesophagus it may be difficult to lower the cardia using an abdominal approach. This may be resolved by truncal vagotomy and the use of a Nissen procedure.

Apart from these complications, the treatment of volvulus is simple and reduction is easy. Resection of the hernial sac does not appear to be obligatory and in difficult cases may result in pleural tears. Reduction of the herniated stomach should be followed by a reduction in the size of the hernial orifice and an antireflux procedure. This was always possible in our series despite the inconsistent quality of the diaphragmatic pillars. Our preference in antireflux surgery is to use the Nissen procedure, but others prefer the Belsey Mark IV procedure undertaken using a thoracic approach[1] The large mobilization of the inferior oesophagus, and especially the freeing of the oesophagus posteriorly, destroys the angle of His and an antireflux procedure appears necessary to prevent postoperative reflux, even if reflux did not exist before operation. The choice of this technique is controversial, however, because in one of our cases it was responsible for postoperative dysphagia. A simple anterior gastropexy, although undertaken quickly, would be expected to be associated with postoperative reflux.

This study shows the seriousness of strangulated intrathoracic gastric volvulus. In one series[6] where ten patients with strangulated volvulus underwent preoperative gastric decompression there were no operative deaths, as opposed to two deaths in four patients with strangulated volvulus where decompression was not possible. Nasogastric decompression was always attempted in our cases, but always failed. Nevertheless, we still consider that preoperative gastric aspiration should always be attempted to prepare the patient for surgery In some cases, temporary relief of engorgement may be possible by endoscopy[3].

In our series, the treatment of intrathoracic gastric volvulus detected in the course of surgery for another acute abdominal problem or during elective surgery for other causes did not appear to affect operative morbidity or mortality. This appears to stress the need for surgery when intrathoracic gastric volvulus is first diagnosed.

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Infrainguinal bypass surgery: factors determining late graft patency

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The results of 373 infrainguinal bypass grafts, in a single centre, between 1980 and 1988 are reviewed. One hundred and thirty in situ *vein (ISV), 47 reversed saphenous vein (RSV), 118 polytetrafluoroethylene (PTFE) and 78 human umbilical vein (HUV) grafts were used. The indications for surgery were disabling claudication in 25 per cent of patients and limb salvage in 75 per cent. In 36 per cent of operations the distal anastomosis was above the knee and in 64 per cent it was below the knee. Overall 5-year patency rates and limb salvage rates respectively were, for ISV (41 and 69 per cent), RSV (62 and 90 per cent), PTFE (31 and 67 per cent) and HUV (29 and 59 per cent). There was no significant difference in patency among these grafts at the above-knee level, but significant differences between vein and prosthetic grafts were evident below the knee* ($P < 0.001$). *Using a proportional hazards model the three factors that consistently correlated with late graft patency were graft type* ($P < 0.001$), *site of distal anastomosis* ($P < 0.001$) *and distal run-off* ($P < 0.001$). *Overall, the results suggest that prosthetic grafts are a suitable alternative to autogenous vein when the distal anastomosis is above the knee, but vein should always be used, if available, below the knee joint.*

Keywords: Peripheral vascular disease, infrainguinal bypass, vascular grafts, patency

Since Goyanes[1] first reported the use of a patient's own peripheral vein to bridge an arterial defect, there has been extensive research into finding a prosthetic graft for arterial bypass which functions as well as the native veins. Nylon grafts appeared in 1956, only to be abandoned shortly afterwards. This was followed by the introduction of Teflon® (E. I. du Pont de Nemours and Company, Wilmington, Delaware, USA) and Dacron® (du Pont) grafts Since their introduction, no other synthetic material has emerged with comparable or better properties, but grafts have improved because of changes in design and manufacturing techniques. Expanded polytetrafluoroethylene (PTFE) was introduced in 1975 and subsequently, because of the poor results of Dacron in infrainguinal bypasses, the use of biological grafts in the form of denatured human umbilical vein (HUV) was revived. At the present time, the three most commonly used conduits for infrainguinal bypass are autogenous vein, PTFE and HUV.

The ultimate fate of infrainguinal bypass grafts continues to be a matter of concern and controversy because grafts in this region exhibit consistently higher failure rates than bypasses in locations such as the aorta. There seems little doubt that, overall, autogenous vein is superior to the alternative prosthetic materials currently available[2], but the relative merits of these options are still controversial. This is a review of all infrainguinal bypass grafts carried out in Leicester Royal Infirmary over the past 9 years, in an attempt to identify the main factors affecting the long-term patency of these grafts.

Patients and methods

Data regarding all patients receiving infrainguinal vascular bypass grafts between January 1980 and December 1988 were retrieved from a vascular database which has been kept in the Leicester Royal Infirmary over this period. Demographic information and risk factors were recorded, together with the initial indication for the bypass. Limb salvage was considered to be the indication when the patient presented with ischaemic rest pain or evidence of tissue necrosis. All patients had preoperative arteriography and the majority had intraoperative arteriography as well Preoperative arteriographic details were obtained from the case records or from the radiographs themselves if no mention of run-off was made in the case records. The main operative details were recorded on the database and this included details of intraoperative arteriograms in the latter half of the study. Intraoperative radiological findings in the earlier years were again obtained from the notes and radiographs The assessment of distal run-off was made from information gleaned from these sources and, as far as we know, all the appropriate data were found. A good run-off was considered to be present when two or three distal vessels were patent and a poor run-off was recorded when there was a single vessel or an isolated popliteal segment During the first half of the study Doppler ultrasound ankle artery pressures were not routinely used during preoperative assessment, although they have been during the latter half. For this reason they have not been included in this review.

Follow-up information was obtained from recent clinic visits. Graft patency was determined by the presence of a palpable pulse in the graft on physical examination or by Doppler ultrasound pressure measurements. Patients without recent follow-up were contacted for re-examination When examination was not possible, information regarding death and limb salvage was obtained from the patient's general practitioner. In cases where recent follow-up was not possible, graft patency was determined at the time of the most recent examination. The results given are those for primary patency as defined by Rutherford *et al.*[3]. Limb salvage is defined as the presence of a viable foot for walking, even if a toe or transmetatarsal amputation was performed.

Statistical analysis was performed by P Burton with software from BMDP Statistical Software, Los Angeles, USA, and consisted of life-tables and survival functions In order to investigate the complex multivariate relationship between a number of factors and the probability of graft occlusion, a multiple regression analysis was performed using the proportional hazards method of Cox[4].

Results

During the period under review 373 infrainguinal bypasses were carried out in 311 patients. The mean age of the patients was 66 years (range 21–92 years) and the male:female ratio was 3:1. One hundred and thirty *in situ* vein (ISV), 47 reversed saphenous vein (RSV), 118 PTFE and 78 HUV grafts were used. There were no differences in the age and sex distribution

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between each graft group. There were, however, significant differences between the groups with respect to level of distal anastomosis and other risk factors (*Tables 1* and *2*). Comparison of graft patencies has, therefore, been assessed according to level of distal anastomosis in order to produce more meaningful results. For example, PTFE grafts terminated at the above-knee popliteal level in 60 per cent of patients but at the tibial level in only 6 per cent. This is in contrast to 4 and 52 per cent respectively for ISV grafts. Three grafts were performed to isolated popliteal segments and all were ISV. About 50 per cent of the HUV grafts were used at the tibial level and, of the 37 grafts performed using this material at this level, 25 were accompanied by a distal arteriovenous fistula. Five further arteriovenous fistulae were constructed, four with ISV and one with RSV, all being at the tibial level. The indication for performing an arteriovenous fistula was lack of continuity of the calf vessels with the pedal arch, as determined on intraoperative arteriography. Some patients also had intraoperative resistance measurements performed, and the levels were always high. The results for all grafts associated with arteriovenous fistula are shown in *Figure 1*. Diabetes was present in 44 per cent of patients with a graft terminating at the tibial level but in only 22 per cent of above-knee grafts. Overall 94 (25 per cent) grafts were performed for disabling claudication and 279 (75 per cent) for limb salvage, the latter indication representing 92 per cent of tibial grafts and 64 per cent of above-knee grafts.

Primary 5-year patency rates are summarized in *Table 3* and are shown according to graft type and level of distal anastomosis. The overall 5-year survival curves for each graft type are shown in *Figure 2*. At 5 years there is no statistically significant difference between the grafts when the distal anastomosis is above the knee. At the below-knee popliteal level (*Figure 3*), autogenous vein is significantly better than prosthetic graft material ($P = 0{\cdot}007$) and this difference is further increased ($P = 0{\cdot}002$) at the tibial level (*Figure 3*). At both above-knee and below-knee levels there is no difference between HUV and PTFE and, where a comparison can reasonably be made (i.e. below the knee) between RSV and ISV, there is again no significant difference.

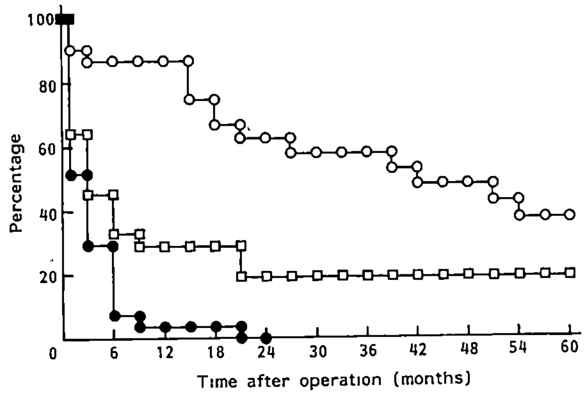
The proportional hazards analysis suggested that four variables were independently and significantly associated with an altered probability of occlusion (*Table 4*). A good run-off (*Figure 4*) was associated with an improved graft survival ($P < 0{\cdot}001$) whilst a prosthetic graft appeared to be associated with an impaired outcome ($P < 0{\cdot}001$). As might be expected, below-knee grafts offered a poorer prognosis than those sited above the knee (*Figure 5*). The risk of occlusion for a below-knee popliteal graft was estimated to be 1·85 times higher than that for an above-knee graft ($P < 0{\cdot}001$), whilst the equivalent risk ratio for a tibial graft was 2·77 ($P < 0{\cdot}001$). There were no interactions between the four covariates in the model and all variables were shown to satisfy the primary assumption of 'proportional hazards'. Although not significant in the multiple regression analysis, diabetics (*Figure 6*) had a poorer overall 5-year patency rate than non-diabetics ($P < 0{\cdot}001$).

Five-year limb salvage rates after bypasses with the different materials were 90 per cent for RSV, 69 per cent for ISV, 67 per cent for PTFE and 59 per cent for HUV.

Table 1 *Distribution of 373 infrainguinal grafts by graft material and level of anastomosis*

Level/material	No.	Percentage of total
Above-knee popliteal		
Reversed saphenous vein	26	19
In situ vein	5	4
PTFE	81	60
Human umbilical vein	24	18
Subtotal	136	36
Below-knee popliteal		
Reversed saphenous vein	13	10
In situ vein	69	53
PTFE	30	23
Human umbilical vein	17	13
Subtotal	129	35
Tibial and peroneal		
Reversed saphenous vein	8	7
In situ vein	56	52
PTFE	7	6
Human umbilical vein	37	34
Subtotal	108	29

PTFE, polytetrafluoroethylene



At risk:											
Patients	30	24	23	17	14	12	12	10	9	7	6
Limbs	30	8	7	4	2	2	2	2	2	2	1
Grafts	30	2	1	1	0	0	0	0	0	0	0

Figure 1 *Cumulative patient survival, limb salvage and graft patency rates for patients with an adjunctive arteriovenous fistula constructed at the time of their femorodistal bypass.* ○, *Patients;* □, *limbs;* ●, *grafts*

Table 2 *Distribution of risk factors among 373 infrainguinal bypasses*

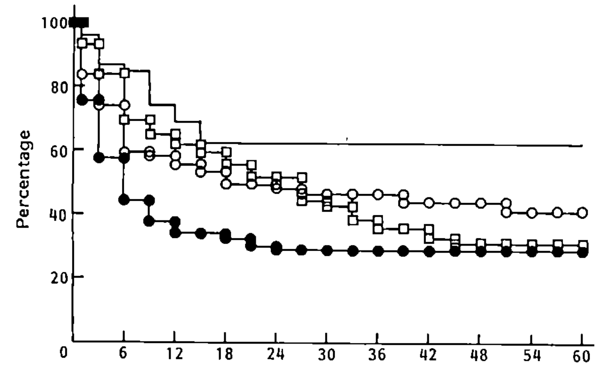
Patient characteristic	Graft material				Run-off		Distal level		
	Reversed saphenous vein	*In situ* vein	PTFE	Human umbilical vein	Good	Poor	Above-knee	Below-knee popliteal	Tibial or peroneal
Diabetic	9	40	20	31	35	65	28	29	43
Non-diabetic	14	33	36	17	70	30	40	37	23
Smoker	17	37	28	18	63	37	37	38	25
Non-smoker	9	32	35	24	57	43	36	31	33
Hypertensive	11	42	33	14	59	41	34	32	34
Normotensive	14	31	31	24	59	41	38	36	26

The values are percentages, PTFE, polytetrafluoroethylene

Table 3 *Primary 5-year patency rates of infrainguinal bypass grafts*

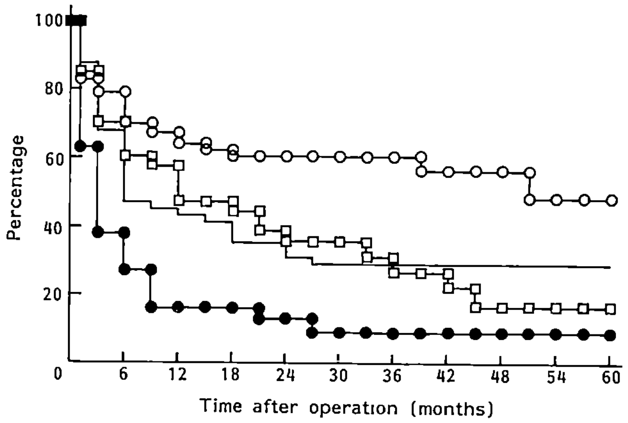
Level	ISV	RSV	Vein (ISV+RSV)	PTFE	HUV	Prosthetic (PTFE+HUV)	All
Above-knee	(80)	63	67	49	54	49	54
Below-knee popliteal	47	60	47	16	27	17	34
Tibial	27	(58)	29	7	10	9	22
All	41	62	42	31	29	30	37

The values are percentages, values in parentheses indicate that the number of grafts performed in these groups was too small to determine reliable patency rates; ISV, *in situ* vein; RSV, reversed saphenous vein; PTFE, polytetrafluoroethylene; HUV, human umbilical vein



At risk:											
RSV	47	34	23	17	16	13	8	5	4	4	3
ISV	130	68	53	39	32	24	19	14	9	4	2
PTFE	118	68	54	43	32	22	14	10	7	4	3
HUV	78	29	20	16	10	7	5	4	3	3	2

Figure 2 *Cumulative primary patency rates for each of the graft types·* ——, *reversed saphenous vein* (*RSV*), ○, in situ *vein* (*ISV*); □, *polytetrafluoroethylene* (*PTFE*), ●, *human umbilical vein* (*HUV*)



82	54	38	31	27	21	16	11	7	3	2
47	24	18	16	10	8	6	5	2	2	1
64	25	19	12	7	4	2	1	1	0	0
44	10	5	5	3	2	0	0	0	0	0

At risk:
- Vein (below-knee popliteal)
- Prosthetic (below-knee popliteal)
- Vein (tibial or peroneal)
- Prosthetic (tibial or peroneal)

Figure 3 *Primary patency rates for autogenous vein* (*in situ vein+reversed saphenous vein*) *and prosthetic grafts* (*polytetrafluoroethylene+human umbilical vein*) *with a below-knee popliteal or tibial or peroneal distal anastomosis.* ——, *Autogenous vein* (*tibial or peroneal*), ○, *autogenous vein* (*below-knee popliteal*), □, *prosthetic graft* (*below-knee popliteal*), ●, *prosthetic graft* (*tibial or peroneal*)

Table 4 *Results of the Cox model for proportional hazards*

Variable	*Estimated risk multiplier*	*95% confidence interval*
Run-off (*good versus* bad run-off)	0·55	0·39–0·77
Graft (prosthetic *versus* vein)	1·77	1·29–2·42
Popliteal level (below-knee popliteal site *versus* above-knee site)	1·86	1·25–2·74
Tibial level (tibial site *versus* above-knee site)	2·77	1·82–4·21

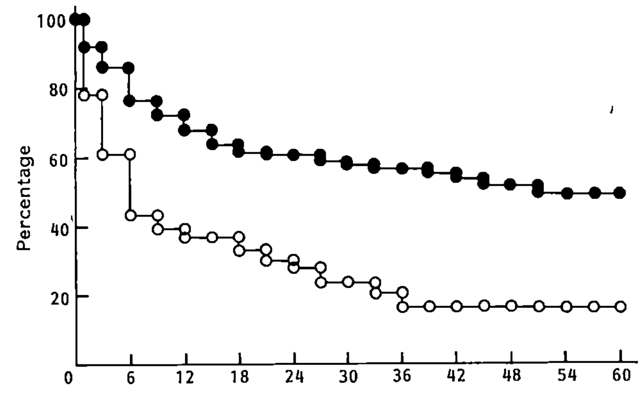
Discussion

These results indicate that the three factors that had the greatest influence on 5-year patency after infrainguinal bypass were graft material, level of distal anastomosis and distal run-off state. Where the distal anastomosis was to the above-knee popliteal there was no difference in patency between autogenous vein and prosthetic grafts. With below-knee anastomoses, however, autogenous vein was far superior to prosthetic materials and this was most evident for tibial bypasses. For grafts reaching below the knee there appeared to be no difference between ISV and RSV, although many more ISV grafts were used, especially for tibial bypasses.

Overall, autogenous vein performs much better than prosthetic materials both in terms of patency and limb salvage, and this is in agreement with other reported series[2,5–7]. As mentioned, at the above-knee level the 5-year patency rate for vein and prosthetic grafts is not significantly different; this was found by Yeager *et al.*[6] and also by Veith *et al.*[2] in a large randomized study. Although Michaels[8] in a recent review of literature on above-knee femoropopliteal bypass grafts over the past 10 years concluded that autogenous vein remains the graft material of choice for all infrainguinal bypass surgery, we continue with a policy of preferentially using prosthetic material for above-knee grafts, reserving the vein for more distal surgery if it becomes necessary. This policy has also been advocated by certain other authors[9], especially for patients with limited life expectancy.

The present results agree with other series[2,5] in showing that vein is much better than prosthetic materials for below-knee bypasses, and this is most marked for tibial or peroneal bypasses. To try to improve the function of prosthetic grafts used for femorodistal bypass, especially when the primary pedal arch is occluded, some surgeons have advocated the use of an adjuvant arteriovenous fistula[10,11]. However, results in this unit using this procedure have been disappointing and it has now been almost totally abandoned here Although such a fistula has been shown to increase graft blood flow and to help maintain graft patency[10,12], there appears to be little benefit in terms of limb salvage[13]. It has also been suggested that interposition of a vein cuff when anastomosing PTFE grafts to small calibre arteries confers haemodynamic advantage and improves patency[14]. A multicentre trial of this 'Miller cuff' is currently underway.

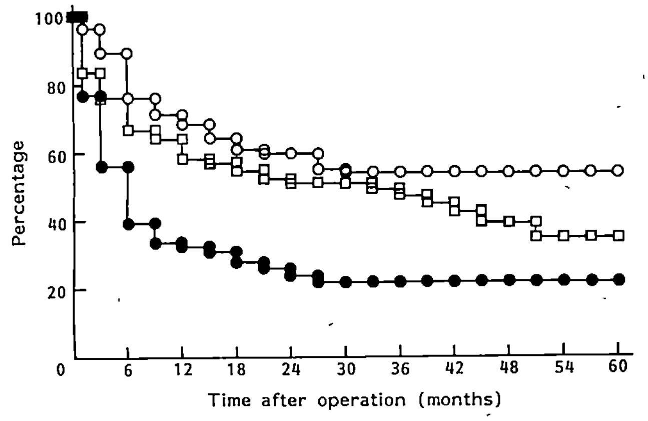
Taken overall, the results seem somewhat disappointing, but



At risk:

Good	215	143	105	80	67	54	42	31	22	14	10
Poor	158	56	44	35	22	11	3	2	0	0	0

Figure 4 *Primary patency rates overall for bypasses with either a good,* ●, *(two or three vessels) or poor,* ○, *(one or no vessel) distal run-off*



Above-knee	136	87	69	52	41	30	21	15	12	8	6
Below-knee popliteal	129	77	55	47	37	29	22	15	9	5	3
Tibial or peroneal	108	35	24	17	10	6	2	1	1	0	0

At risk.
Above-knee
Below-knee popliteal
Tibial or peroneal

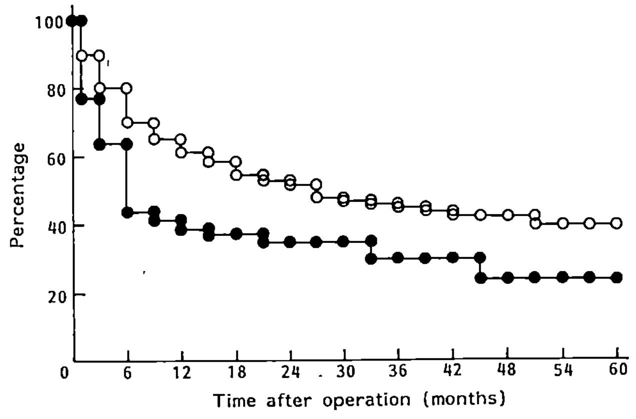
Figure 5 *Primary patency rates overall according to level of distal anastomosis.* ○, *Above-knee popliteal;* □, *below-knee popliteal;* ●, *tibial or peroneal*

there are only a few other studies with which to compare patencies at 5 years. In those that report patencies at 5 years, the results using prosthetic graft materials appear similar. Results in the present series for PTFE compare favourably with one of the few reports from the UK, by Williams *et al.*[15], in which the 4-year patency rate with PTFE was only 18 per cent. Reports from centres in the USA show no better results, with Charlesworth *et al.*[16] reporting a 6-year patency rate of only 24 per cent and Rutherford *et al.*[5] a patency rate of 35 per cent at 3 years. For PTFE grafts below the knee, the results are universally poor[16–18], and HUV seems to fare little better[5] although there have been a few series that have reported slightly more encouraging results using this material[17,19,20]. One of the main drawbacks of using HUV grafts, however, is the biodegradation that they undergo, leading to dilatation and aneurysm formation. Dardik reported the incidence of aneurysm at and beyond 5 years to be at least 36 per cent[21], although in the present series only one graft had to be removed because of a large aneurysm. The overall incidence of dilatation and aneurysm formation in this series is not known because routine follow-up did not include ultrasound imaging. On the whole PTFE and HUV grafts perform equally badly below the knee.

A patency rate of 67 per cent at 5 years for autogenous vein bypasses in the above-knee position compares favourably with other series[2,6,22,23]. Most reports of vein in the below-knee position are from the USA and most in addition give the secondary patency rates rather than the primary rates as in the present study. The reports from the UK are a little difficult to compare with the present results because patencies are not quoted according to the site of distal anastomosis. Grimley *et al.*[24] quote a 70 per cent 5-year patency rate for RSV, and Harris *et al.*[25] give a 3-year patency rate of 77 per cent for RSV and of 68 per cent for ISV grafts. However, both of these studies combine above-knee and below-knee grafts. This is also the case with Denton *et al.*[26] who reported a patency rate of 72 per cent for ISV, but only at 18 months. Beard *et al.*[27] reported a 3-year patency rate of 55 per cent for ISV grafts below the knee and this figure is slightly better than our 3-year value of 45 per cent, but again Beard *et al*'s data represent secondary patency. In that study they also noted a trend towards lower patency rates in veins with a minimum diameter of less than 4 mm, although this did not reach significance because the total number of grafts was too small. Vein diameters were not routinely measured in our study.

In comparison with the reports from the USA, the present results do not compare favourably, especially for ISV. Leather *et al.*[28] in a large series of 1000 ISV grafts reported a 5-year patency rate of 78 per cent for below-knee popliteal and of between 62 and 79 per cent for more distal bypasses, depending on the vessel used. These were, however, secondary patencies. Karmody *et al.*[29] reported patency rates of between 64 and 69 per cent at 4 years for tibial and peroneal bypasses with ISV. For RSV, Kacoyanis *et al.*[30] quoted a 5-year patency rate of 46 per cent for tibial and peroneal grafts, and although the present figure of 58 per cent compares well with this, insufficient bypasses have been performed using RSV in this position to make a valid comparison. The results presented here for RSV as femoropopliteal bypasses are, however, similar to those reported in some of the other American series[23,31].

As stated previously, there appeared to be no difference between RSV and ISV grafts below the knee. In the one prospective, randomized study comparing these two conduits, Harris *et al.*[25] also found no significant difference. On the other hand, in a separate study, Rutherford *et al.*[5] found that while this was the case for below-knee popliteal grafts, for tibial and peroneal grafts ISV appeared to be better than RSV. This was not a randomized study. In theory the *in situ* technique has advantages over reversed vein in more distal bypasses, not least because the anastomoses are carried out with vessels of similar



Non-diabetic	256	161	121	96	76	56	39	27	18	11	8
Diabetic	108	38	28	19	12	9	6	5	4	3	2

At risk:
Non-diabetic
Diabetic

Figure 6 *Effect of diabetes on overall patency of infrainguinal bypass grafts.* ○, *Non-diabetic;* ●, *diabetic*

diameter Operators in the present study tended to use ISV rather than RSV grafts below the knee, mainly because of the comparable size of the vessels involved at the anastomoses. There is no evidence, however, that the *in situ* technique confers any haemodynamic advantage[32,33].

The risk factors with the greatest bearing on graft patency have already been described. Although distal run-off from the below-knee popliteal can usually be determined from preoperative arteriograms, these rarely give good views of the vessels of the distal calf and beyond. It is therefore difficult to determine before operation the patency of the pedal arch and continuity of calf vessels into the arch. This continuity appears to be an important determinant in graft patency[34]. It can be determined by intraoperative arteriography, but the recently introduced method of intra-arterial digital subtraction arteriography seems to be useful in preoperative assessment. This facility will become available in Leicester in the near future. The use of pulse-generated run-off[35] has, however, recently been introduced for preoperative assessment as a means of documenting run-off more fully.

It is interesting to note that smoking does not appear to be an important risk factor in this series. However, as in many studies, these figures are based on direct questioning of patients, which is known to be unreliable because many patients are untruthful about their smoking habits. If one is to obtain more realistic figures, smoking markers, such as thiocyanate, should be measured[36]. It might also have been more informative to distinguish between smoking before and after operation. Details of this were not always available. Although diabetes appears to be a significant risk factor in the univariate analysis, when proportional hazards analysis is performed it is no longer significant. This occurs because diabetic patients tend to have poorer run-off and also have more distal grafts; these are both highly significant factors in the proportional hazards model.

As in many studies, the limb salvage rate is considerably higher than the graft patency rate. There are two possible reasons for this. Firstly, patients who have grafts for claudication rarely lose the limb if the graft occludes. Secondly, in those for whom the indication is limb salvage, even if the graft functions for only a short period, it may allow ulcers or transmetatarsal amputations to heal If the graft later fails, it is of less significance because the limb has already been saved. In the present study the majority of limb losses occurred when grafts failed within the first month in those patients undergoing surgery for limb salvage.

In summary, in above-knee femoropopliteal bypasses prosthetic grafts are an acceptable alternative to autogenous vein. In this position a case can be made for using them preferentially, especially when operation time needs to be minimal or when there is a likelihood of future, more distal, surgery. For grafts that reach below the knee, however, every effort should be made to use autogenous vein. When such vein is not available prosthetic grafts provide an alternative to amputation in selected patients.

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Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £200.00. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Edinburgh EH3 9YW, UK.

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Popliteal aneurysms identified by intra-arterial streptokinase: a changing pattern of presentation

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Five patients presenting with chronic or subacute leg ischaemia due to thrombosed popliteal artery aneurysm are described. Only one of these aneurysms was diagnosed before intra-arterial streptokinase infusion, which successfully lysed the thrombus in all cases. One aneurysm had been symptomatic for 5 years and another for 2 years. Popliteal aneurysm may well be underdiagnosed as a cause of chronic leg ischaemia.

Keywords: Popliteal aneurysm, streptokinase, thrombolytic therapy

Thrombosed popliteal aneurysm is a well recognized cause of an acutely ischaemic leg$^{1-5}$. It is generally accepted, however, that the majority of these aneurysms are asymptomatic. About one-third will produce acute ischaemia due to thrombosis or distal embolization$^{2-4}$, and claudication occurs in 5–41 per cent$^{2-4}$. In fact, popliteal aneurysm may be responsible for a much larger proportion of claudicants than has previously been recognized: silent chronic thrombosis might result in symptoms of claudication that are indistinguishable from those produced by atherosclerotic occlusion.

Clinical details

Between October 1988 and December 1989 intra-arterial streptokinase was used in selected cases of acute and chronic arterial occlusion. Of 40 patients, five men were discovered to have thrombosed popliteal aneurysms. In four of these patients, the initial presentation was claudication; a popliteal aneurysm was palpable in only one case. The diagnosis was suspected from the initial intravenous digital subtraction angiogram in only two cases (because of a contralateral aneurysm). All five were successfully lysed with intra-arterial streptokinase and subsequently all patients had ligation and bypass operations.

After clinical and Doppler ultrasound assessment, each patient had intravenous digital subtraction angiography. Formal arteriography was then performed under local anaesthesia, and a catheter was left *in situ* for streptokinase infusion. Either the ipsilateral or the contralateral femoral artery was used. The rate of infusion was 10000 units streptokinase plus 500 units heparin per hour. Follow-up arteriography was performed at regular intervals (approximately 6–12-hourly) until satisfactory clot lysis had occurred. Patients were then fully heparinized until bypass operation. Details of the patients are given in *Table 1* and angiograms from case 1 are shown in *Figures 1–3*.

Two of the five patients presented with long-standing, gradually worsening, intermittent claudication while the remainder had acute on chronic ischaemia, developing over 4–12 weeks.

Discussion

Systemic thrombolysis for peripheral vascular disease using intravenous streptokinase was first used in the early 1960s and, although it was of some value, the complication rate in terms of haemorrhage and allergic reaction was high$^{6-9}$. Low-dose intra-arterial thrombolysis with streptokinase, urokinase or tissue plasminogen activator was introduced in the 1970s^{9} and the use of intra-arterial streptokinase is becoming an accepted

Table 1 *Symptoms and outcome for five patients with popliteal aneurysm treated with intra-arterial streptokinase before bypass operation*

					Popliteal aneurysm			
Patient no.	Age (years)	Symptoms and duration	Doppler ankle/brachial index	Duration of streptokinase treatment (h)	Nature	Diameter (relative to superficial femoral artery)	Outcome	Duration of follow-up (months)
1	62	8 weeks' leg ulceration, 1 day of rest pain	0·25	36	Fusiform	×3·0	Foot pulse restored, contralateral aneurysm by-passed 3 months later	8
2	59	2 years' claudication, becoming incapacitating	0·40	96	Fusiform	×3·5	No pulse initially, graft occluded, re-explored, foot pulse restored	8
3	65	5 years' claudication, walking distance reduced to 50 m	0·44	120*	Saccular	×2·5	Foot pulse restored	4
4	61	3 months' claudication, 1 day of rest pain	0·16	36	Fusiform	×2·0	Foot pulse restored, contralateral aneurysm thrombosed 6 weeks later, bypassed after thrombolysis with tissue plasminogen activator	4
5	78	4 weeks' claudication, 1 day of rest pain	0	24	Saccular	×5·0	Foot pulse restored	4

*Aneurysm apparent at 24 h, although the calf vessels not fully cleared until 120 h

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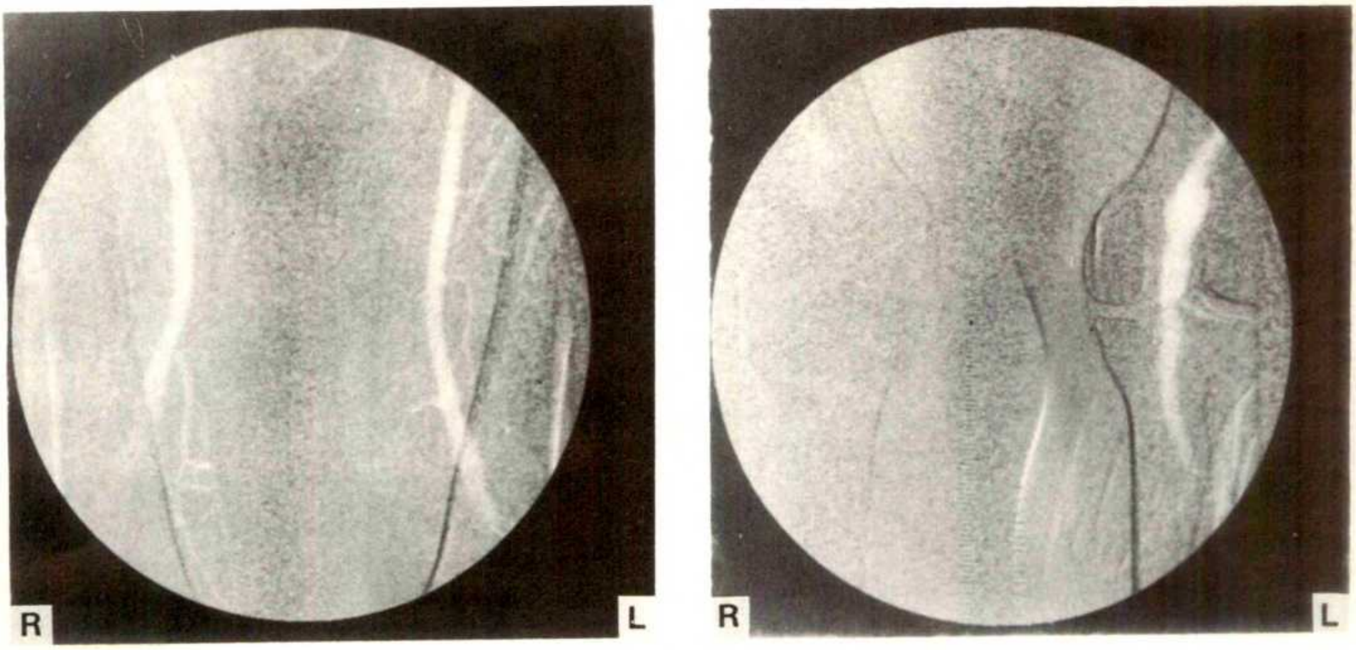

Figure 1 *Intravenous digital subtraction angiograms showing a left popliteal aneurysm* (*left*) *and an occlusion of the right superficial femoral artery at the adductor hiatus, with no run-off* (*right*)

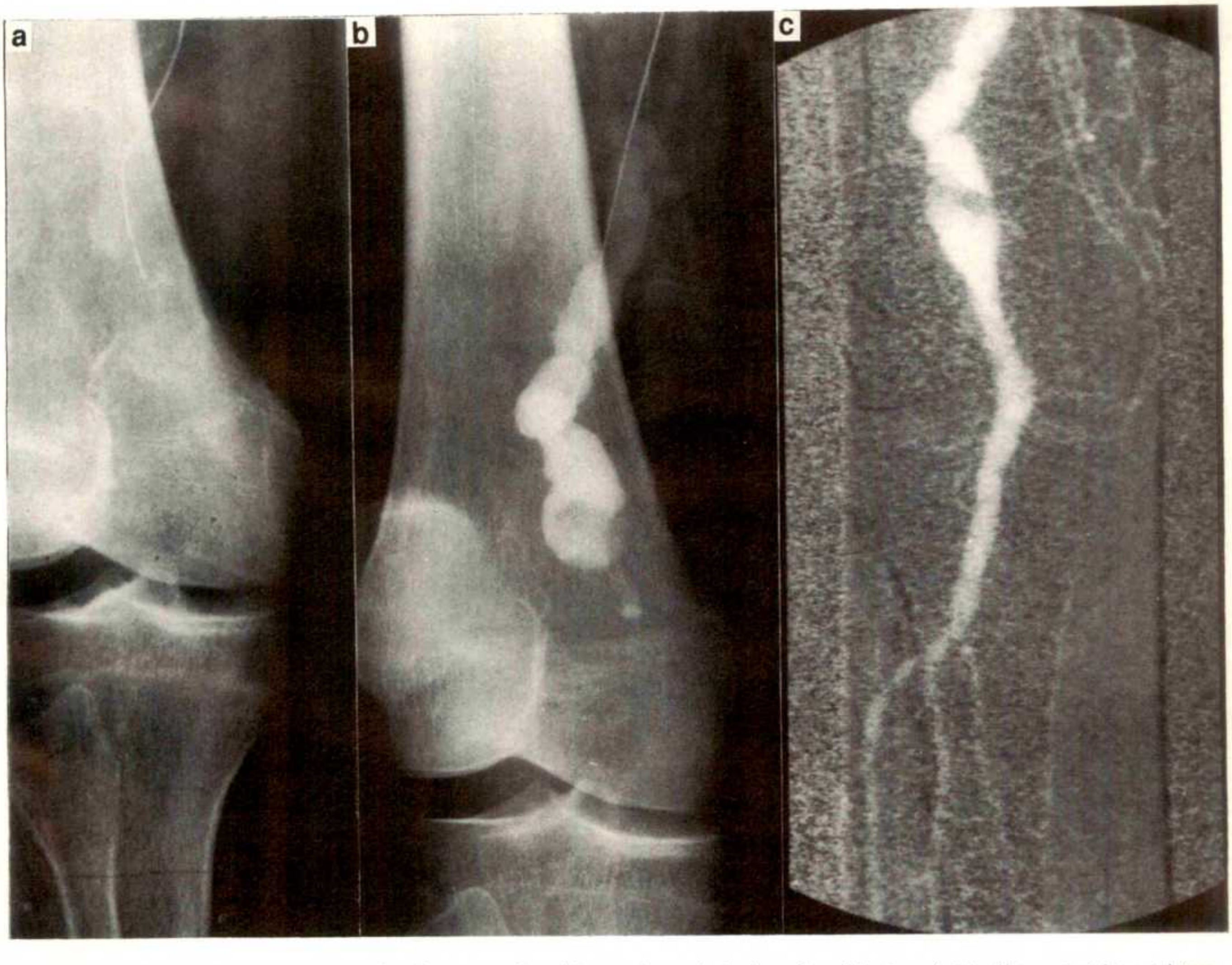

Figure 2a *A perfusing catheter and guide-wire have been inserted, and the complete occlusion is confirmed;* **b** *after only 4 h of intra-arterial streptokinase therapy the popliteal aneurysm is clearly visible;* **c** *after 36 h the calf vessels are clear of thrombus*

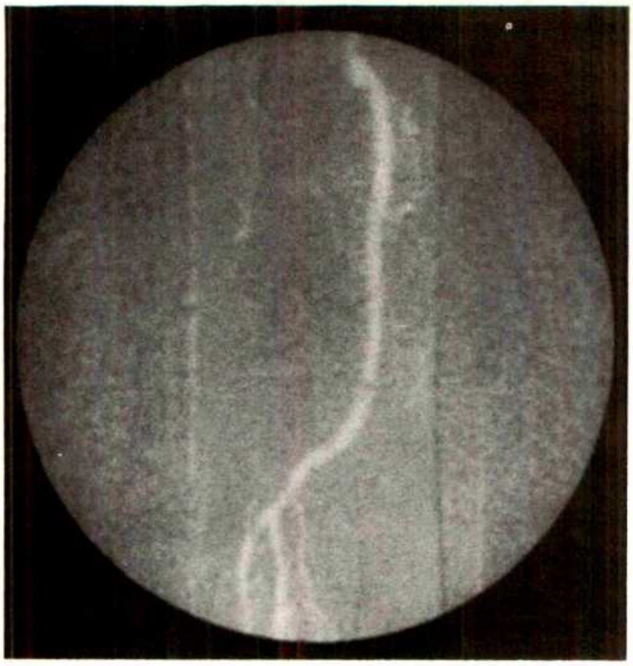

Figure 3 *After operation the intravenous digital subtraction angiogram shows that the popliteal aneurysm has been successfully ligated and bypassed*

technique for the treatment of acutely ischaemic limbs[6–10]. It has also been used with more limited success in chronic occlusion, but although Lammer *et al.* treated 47 patients with this condition no thrombosed popliteal aneurysms were discovered[10].

The definition of popliteal aneurysm is imprecise but tends to be based on an arterial diameter of more than 2 cm. Having made the diagnosis in this series of cases no further attempt was made to measure the sizes of the lesions with either ultrasonography or computed tomography. However the internal diameters of the aneurysms, as seen on angiography, were between two and five times greater than the internal diameter of the patients' superficial femoral arteries. The possible diagnosis of popliteal aneurysm was considered in each case on presentation. In only one case was the aneurysm convincingly palpated before the vessels were cleared by thrombolysis.

Popliteal aneurysm usually occurs in elderly patients, the vast majority (90–97 per cent) being men[1–4]. The disease occurs bilaterally in 33–68 per cent of patients and up to 40 per cent have an associated abdominal aortic aneurysm[1]. Complications are usually due to thrombosis of the aneurysm or distal embolization of thrombus giving rise to a gradation of symptoms from claudication to severe ischaemia. Symptoms may also be due to local compression, but rupture is rare.

The results of operating on asymptomatic aneurysms are excellent, especially if autologous saphenous vein is used, with 95 per cent 10-year graft patency[2]. Limb loss is rare. A good outcome can be predicted if one or more foot pulse is palpable after operation[2]. If left alone, approximately 30 per cent will deteriorate and require operation[2,3], although this figure may be as low as 8 per cent for very small aneurysms[4].

By contrast, in the limb which is severely ischaemic due to blockage of the tibioperoneal trunk initial operative success is lower and early graft failure is more common[2,3]. Amputation rates range from 16 to 50 per cent despite operation[3,4] and mortality rates are high. These poor results are partly due to lack of run-off, but they may also be due to delay in diagnosis or even to overlooking the diagnosis completely.

In two of the present cases intravenous digital subtraction angiography showed a contralateral popliteal aneurysm and therefore it was thought likely that a similar problem might exist on the affected side. In two cases intermittent claudication had been present for years, and none of the remainder had an acutely ischaemic, non-viable limb. The more widespread use of intra-arterial streptokinase might result in more occluded popliteal aneurysms being diagnosed in patients thought to have ischaemia due to long-standing occlusive disease.

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Extradural haematoma in the Irish Republic: an analysis of 82 cases with emphasis on 'delay'

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Eighty-two cases of extradural haematoma were analysed to elucidate the factors contributing to delay in treatment and poor outcome. The majority of cases occurred in the first three decades of life with falls being the commonest aetiological factor. Five distinct modes of presentation are described. Excessive delay occurred in recognizing the condition and in subsequent transfer of patients. This resulted in many patients being operated on while in coma. Associated intracranial and extracranial injury occurred in a significant number of cases. Recommendations for the management of these patients are outlined.

Keywords: Extradural haematoma, computed tomographic scan, delay, outcome, lucid interval

Post-traumatic extradural haematoma is a frequently encountered, life-threatening but readily remediable condition. Delay in treatment is an important factor contributing to poor results[1]. The wide availability of computed tomographic (CT) scanning in the late 1970s and early 1980s should have made a marked difference in reducing delay by providing rapid and early diagnosis. Seelig *et al.*[2] and Lobato *et al.*[3], however, in their recent series still report depressingly high mortality rates for patients operated on in coma.

Only two neurosurgical units exist in the Republic of Ireland and the lack of a motorway network makes transfer of patients time consuming. Our unit in Cork serves a catchment population of approximately one million people and receives patients from numerous peripheral general hospitals (*Figure 1*). Because many of our patients thereby suffer delay in coming to surgery, we undertook this study to analyse the southern Irish experience with particular reference to the pattern of referral and the associated outcome.

Patients and methods

CT scanning became available in Cork in October 1979. Between January 1980 and June 1989, 87 patients underwent craniotomy for evacuation of extradural haematoma in our unit. Adequate documentation was available in 82 cases, which form the basis of this report. Small haematomas (fracture haematomas) have been excluded from consideration. Because our hospital is a designated trauma centre, there is minimal delay to surgery, with craniotomy beginning within 1 h of arrival.

'Lucid interval' was defined as the time from injury or recovery from initial unconsciousness to subsequent deterioration in consciousness. Outcome was defined according to the Glasgow Outcome Scale[4]. Referrals were classified into three groups:

(1) Inhospital referrals: in our hospital only patients with serious head injuries are admitted to the department of neurosurgery; all others are admitted to the accident and emergency ward with neurosurgical consultation as requested.
(2) Interhospital referrals: patients who were transferred from other hospitals to our unit.
(3) Direct referrals: patients who were admitted directly to our unit from the accident and emergency department.

Results

There were 73 men and nine women. In common with other series many patients (27 patients, 33 per cent) were in the 11–20 years age group. The zero–10 years age group accounted for 20 (24 per cent) cases. The condition was rarely encountered in patients older than 50 years of age (seven cases).

Falls accounted for the largest number of cases (44 per cent) with road traffic accidents relegated to second place (33 per cent). Assaults, sports and industrial accidents accounted for the remainder. Alcohol was an associated factor in 21 (26 per cent) cases.

Modes of presentation

Five distinct modes of presentation may be described in respect of changes in the level of consciousness observed in the evolution of the condition[5].

(1) Group 1 (eight cases, 10 per cent): patients who sustained no initial loss of consciousness and who remained fully conscious until the time of treatment.
(2) Group 2 (39 cases, 48 per cent): patients who sustained no initial loss of consciousness but who subsequently deteriorated.
(3) Group 3 (six cases, 7 per cent): patients who were initially unconscious but recovered and remained alert or relatively so until time of treatment.
(4) Group 4 (13 cases, 16 per cent): patients who were initially unconscious, recovered for a lucid interval and subsequently deteriorated again.

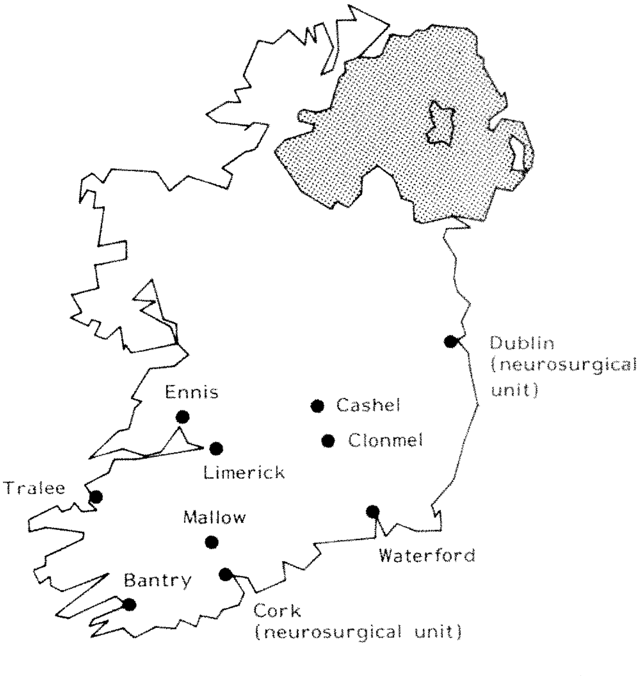

Figure 1 *Map outlining the centres of referral to the neurosurgical unit*

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(5) Group 5 (16 cases, 20 per cent): patients who were unconscious from the outset and did not at any time regain their senses before treatment.

The duration of the lucid intervals is shown in *Table 1*. In over 50 per cent of cases it was less than 6 h. In 8 per cent of cases there was a lucid interval of more than 24 h.

Pattern of referral

Table 2 lists the sources of referral and their accompanying distances from our unit. Sixty-one per cent were interhospital referrals. The transfer time and the associated deterioration in level of consciousness for 46 patients exhibiting a lucid interval of known duration are shown in *Table 3*. Note that although all patients were alert at some stage after the injury, 27 (59 per cent) arrived in our unit in coma. In 50 per cent of cases of interhospital referral the transfer time was longer than 5 h. In our own hospital seven out of 11 patients were allowed to deteriorate into coma before appropriate treatment was undertaken.

Six cases not described in *Table 3* are discussed below. Case 1 involved a patient who received a blow to the head with momentary loss of consciousness 1 week before presentation. He was well in the intervening period until he suddenly collapsed into coma. On admission to the referring hospital he had a Glasgow Coma Score of 3 with bilateral unreactive pupils. Transfer time was 4 h.

Table 1 *Analysis of lucid interval in 52 patients*

Duration of lucid interval (h)	No. of cases
0–1	8 (15)
>1–3	11 (21)
>3–6	9 (17)
>6–12	9 (17)
>12–24	5 (10)
>24	4 (8)
Unknown	6 (12)

Values in parentheses are percentages

Table 2 *Sources of referral*

Source	Distance (km)	No. of cases
Direct/ in hospital	–	32
Limerick	105	12
Cork	–	8
Cashel	96	8
Tralee	119	6
Ennis	137	5
Waterford	126	4
Bantry	90	3
Mallow	33	2
Clonmel	90	2

Table 3 *Deterioration in level of consciousness and the associated time interval to arrival in the neurosurgical unit from the moment of first concern in 46 patients with extradural haematoma*

		Glasgow Coma Score on arrival			Time elapsed (h)		
Source	No. of cases	3–4	5–8	9–15	0–3	>3–5	>5
Direct	12	3	4	5	7	3	1
Interhospital	23	6	7	10	5	5	10
Inhospital	11	3	4	4			

Six unusual cases are discussed separately in the text

Table 4 *Summary of patients with no deterioration in consciousness*

Patient no.	Reason for referral	Duration from injury to surgery
1	Continued headache	4 days
2	Increasing headache	17 h
3	Vomiting	12 h
4	Skull fracture with lateralizing signs	5 h
5	Skull fracture with increasing headache	5 days
6	Depressed skull fracture	36 h
7	Bleeding from ear	18 h
8	Agitation	5 h

Table 5 *Summary of patients with immediate loss of consciousness and subsequent recovery to lucidity*

Patient no.	Reason for referral	Duration from injury to surgery
1	Increasing headache	5 days
2	Increasing headache	1 day
3	Generalized seizure	4 h
4	Increasing hemiparesis	2 days
5	Cerebrospinal fluid rhinorrhoea	2 days
6	Unknown	Unknown

Case 2 involved a known epileptic who was admitted to the referring hospital after recovering from a seizure. Over the next 24 h he deteriorated into coma with a unilateral unreactive pupil. He was treated for status epilepticus and underwent a lumbar puncture. Transfer time was 72 h.

Case 3 was a patient who had elevation of a depressed skull fracture in the referring hospital. Over the next 24 h he deteriorated into coma with a unilateral unreactive pupil. On our instructions the wound was reopened and the patient was transferred. Transfer time was 2 h, by helicopter.

Case 4 involved a patient who underwent craniotomy in the referring hospital for a clinical diagnosis of extradural haematoma. He failed to recover consciousness in the postoperative period and was transferred. Transfer time was 24 h.

Case 5 was a patient who underwent craniotomy in the referring hospital for a clinical diagnosis of extradural haematoma. Adequate haemostasis could not be achieved and he was transferred. Transfer time was 10 h.

Case 6 involved a patient who rapidly deteriorated in the referring hospital. Burr-holes were made on our instructions. Transfer time was 6 h.

Table 4 is a summary of the group 1 patients with no deterioration in level of consciousness. Headache and skull fracture were the predominant reasons for referral.

Table 5 is a summary of the group 3 patients who had an initial loss of consciousness but with a sustained recovery. Note the variation in the reasons for referral and the long referral time of 5 days in one case.

The reasons for and duration of referral for group 5 patients with an immediate loss of consciousness without recovery to lucidity are shown in *Table 6*. Coma and drowsiness associated with a skull fracture were the most frequent reasons for referral. Eleven (69 per cent) cases took 5 h or more to reach our unit: indeed in four cases the delay was as great as 2 days or more.

Associated injuries

Associated intracranial injuries occurred in 22 (27 per cent) cases and the manifestations included cerebral contusion (15 cases), intracranial air (three cases), acute subdural haematoma (two cases) and intraventricular haemorrhage (one case). One patient required two craniotomies, one for an extradural

Table 6 *Summary of patients with immediate loss of consciousness without recovery to lucidity*

Patient no.	Reason for referral	Duration from injury to surgery
1	Coma (3)	12 h
2	Coma (3)	3 h
3	Coma (3)	Unknown
4	Coma (8)	Unknown
5	Coma (7)	3·5 h
6	Direct (8)	<1 h
7	Drowsy with skull fracture (9)	16 h
8	Drowsy with skull fracture (10)	3 days
9	Drowsy (7)	9 h
10	Drowsy with skull fracture (10)	5 h
11	Drowsy with skull fracture	5 h
12	Drowsy (11)	2 days
13	Drowsy (13)	2 days
14	Drowsy (13)	2 days
15	Extradural clot found at exploratory burr-hole	6 h
16	Direct	6 h

Values in parentheses are Glasgow Coma Scores at first contact

Table 7 *Associated extracranial injury in 16 patients*

Injury	No. of patients
Fractured cervical spine	1
Fractured long bone	3
Fractured clavicle	4
Dislocated hip	1
Fractured base of skull with facial nerve palsy	1
Fractured mandible	1
Fractured zygoma	1
Penetrating eye injury	1
Caroticocavernous fistula	1
Fractured ribs with pneumothorax	2

haematoma and the second for a contralateral intracerebral haematoma.

Associated extracranial injury occurred in 16 (20 per cent) cases and consisted predominantly of long bone fractures and facial injuries (*Table 7*).

Outcome

Analysis revealed a good outcome in 66 cases (80 per cent), moderate disability in four (5 per cent), severe disability in two (2 per cent), persistent vegetative state in four (5 per cent) and death in six (7 per cent). Late post-traumatic epilepsy occurred in three cases and one patient required a ventriculoperitoneal shunt for hydrocephalus. Bone flap infection occurred in two cases.

In three of the six deaths avoidable factors contributing to a fatal outcome were uncovered. One patient exhibited a 'classical' lucid interval but for some inexplicable reason was observed in our unit until he deteriorated into coma before undergoing a computed tomographic scan. A second patient who had no haematoma on her admitting CT scan was allowed to deteriorate into coma before a repeat CT scan revealed a massive (150 g) haematoma 8 h later. The third patient was transferred from another hospital in coma 6 h after we urgently requested his transfer.

Excessive delay in transfer (6 h and 5 h) occurred in two cases, contributing to their persistent vegetative state.

Discussion

Post-traumatic extradural haematoma occupies an important place in the spectrum of head injuries. It occurs relatively frequently, predominantly in young people, and often results in death or severe disability. With increasing leisure time and motorized transport its frequency will almost certainly increase. CT scanning has revolutionized the diagnosis and the condition is readily dealt with in a neurosurgical unit. In spite of the optimism of Bricolo and Pasut[6] most of the larger series report a mortality rate greater than 10 per cent[2,3,6–9]. There is no doubt that delay to surgery is responsible for the majority of poor results. Lobato *et al.*[3] elegantly demonstrated the correlation between coma, extensor posturing, pupillary changes and death. With the special circumstances in the Republic of Ireland we examined our experience to see if the management of these patients could be improved.

The study demonstrated that the demographic features of extradural haematoma here are similar to those reported elsewhere with 78 per cent of cases occurring in the first three decades of life. Falls and road traffic accidents were responsible for most cases. Associated intracranial injuries occurred in a relatively large number of cases (27 per cent). Furthermore associated extracranial injuries, often overlooked in a deteriorating patient, occurred in 20 per cent of cases and were often of a serious nature.

Analysis of the modes of presentation revealed that the classical lucid interval, so often taught to undergraduates, occurred in a mere 16 per cent of cases (group 4). The most frequent mode of presentation was 'no initial loss of consciousness but with subsequent deterioration' (group 2, 48 per cent). This group also exhibited a lucid interval albeit not of the classical type. Overall 63 per cent of patients exhibited a lucid interval, an important diagnostic indicator when present.

The corollary, of course, is that over a third of patients had no lucid interval. In 20 per cent of cases the patient was never lucid, while in 10 per cent no deterioration in consciousness occurred. Further analysis revealed that in 8 per cent of cases the lucid interval was longer than 24 h, a period which is the usual duration of hospital stay for patients admitted for head injury observation. Note than in 15 per cent of cases the lucid interval was less than 1 h, indicating the need for urgent treatment.

The pattern of referral demonstrated some disturbing features. In cases exhibiting a lucid interval, 66 per cent of interhospital referrals and 64 per cent of inhospital referrals were operated on in coma. Delay occurred at two levels: 50 per cent of interhospital referrals took longer than 5 h to arrive in our unit indicating undue delay in transfer; the pattern of inhospital referral identifies a delay in recognition and we may assume that the same applies to interhospital referral, further adding to the delay. At least two factors contribute to delay in recognition: (1) attribution of a depressed level of consciousness to alcohol intoxication[10]; and (2) lack of awareness of guidelines issued by a group of neurosurgeons on the management of head injuries[11,12].

Six patients were operated on in the referring hospitals for rapidly deteriorating consciousness. In only two cases, however, was our advice sought before operation. The resultant delay was excessive in the four other cases. The majority of patients in group 5, i.e. those who were never lucid at any stage, also took more than 5 h to reach our unit.

Patients in groups 1 and 3, i.e. those with no loss of consciousness and those with a sustained recovery from initial loss of consciousness, were of interest. Increasing or sustained headache was the referring symptom in over one-third of the cases. In one case the diagnosis was made 5 days after the injury.

In spite of the excessive delay to surgery in many cases, our mortality rate is one of the lowest reported. Indeed if there were no errors in the management of this series of patients the mortality rate would have been 4 per cent, thus approaching the elusive zero. We could not identify the reasons for our favourable results except that we insist on rapid access to CT scanning and use it frequently in head-injured patients. A normal CT scan within 6 h of injury does not preclude the diagnosis[13]. This important point was responsible for one fatality in our series. We also provide a continuous advisory service to our accident department and constant telephone availability to all hospitals in our drainage area. We have our operating theatre on constant standby and can be operating within 40 min of arrival. This creates expensive and consuming demands on nursing, anaesthetic and surgical staff but we feel that the need and results justify the costs involved. It is very gratifying to see patients operated on at an early stage sitting up in bed the next day, in contrast to those patients whose treatment was delayed with the inevitable penalties of prolonged hospital stay, increased morbidity and permanent neurological deficit.

Recommendations

1. The different modes of presentation of extradural haematoma should be stressed in undergraduate and postgraduate teaching.
2. The elucidation of a lucid interval in a head injured patient demands urgent action.
3. The guidelines issued by a group of neurosurgeons[11] should be prominently displayed in all accident and emergency rooms.
4. Computed tomographic scanning should be used liberally in patients with head injury.
5. Patients suspected of harbouring an extradural haematoma must be rapidly transferred to a neurosurgical unit.
6. Neurosurgical advice should be obtained before embarking on emergency operations outside specialists centres.

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Extracorporeal gas exchange in adult respiratory distress syndrome: associated morbidity and its surgical treatment

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Extracorporeal carbon dioxide removal ($ECCO_2$-R) over a membrane lung is a new therapy for patients with adult respiratory distress syndrome (ARDS) who frequently suffer from lung complications caused by long-term artificial ventilation and who may require major thoracic surgery. This is a report of 76 patients with severe ARDS who were treated by $ECCO_2$-R. Twenty-six of these 76 patients required thoracotomy: 19 for pneumothorax and pneumatocele, and seven for haemothorax, infected lung necrosis or oesophagotracheal fistula. Most pneumothoraces were bilateral. Ten of these 26 patients required reoperation, usually for extensive persisting alveolar air leaks. Sixteen (62 per cent) of the 26 patients who had a thoracotomy and 22 (44 per cent) of the 50 patients without surgery survived. These results demonstrate that performing a thoracotomy, if necessary, does not diminish the survival chance of high-risk patients with severe ARDS.

Keywords: Pulmonary barotrauma, thoracotomy, extracorporeal carbon dioxide removal, long-term ventilation, adult respiratory distress syndrome

Adult respiratory distress syndrome (ARDS) is defined as an acute arterial hypoxia caused by an increased intrapulmonary shunt, decreased compliance of the lung, infiltrates seen on chest radiography and normal capillary wedge pressure[1]. Using these parameters Morel *et al*. classified respiratory failure into four grades[2] (*Table 1*). The aetiological factors in surgical patients include sepsis, haemorrhagic shock, trauma, aspiration, fat embolism and pneumonitis. Current therapy consists of mechanical ventilation with elevated levels of oxygen and high levels of positive pressure. Although the pulmonary-related mortality rate in ARDS is low at moderate grades of respiratory failure, by stage 4 mortality rates using conventional respiratory therapy range from 70 to 90 per cent[3,4].

In 1980 Gattinoni and co-workers reported success with extracorporeal carbon dioxide removal ($ECCO_2$-R) as a new therapy for severe ARDS[5]. Using this high technology equipment the mortality rate can reduce to about 50 per cent[5,6]. Because most of the patients are young and their pulmonary function returns to normal the high cost of the therapy (about 5000 Deutschmarks or 1800 pounds sterling daily) may be of secondary importance. $ECCO_2$-R is based on experimental studies in animals performed by Kolobow *et al.* who demonstrated that the physiological gas exchange of the lung can be dissociated: oxygenation may occur from bronchoalveolar oxygen flow with low frequency positive pressure ventilation in an almost tranquilized lung, while carbon dioxide removal is performed extracorporeally by a membrane lung[7]. This relieves the ARDS patient from the harmful high pressure artificial ventilation which would otherwise be necessary. Tranquilization of the lung is said to help the damaged organ to a better and quicker recovery. Implantation of a venovenous bypass is necessary for $ECCO_2$-R. Early systems required full systemic heparinization which led to specific complications such as haemorrhage into the lung or to haemothorax. New systems with covalently bound heparinized lines should minimize these bleeding complications.

More frequent and severe complications occur from long-term ventilation which produces specific pulmonary barotrauma. This is seen in patients undergoing $ECCO_2$-R and, indeed, in all long-term artificially ventilated patients. The occurrence of barotrauma depends on the severity of ARDS, the duration of artificial ventilation, the level of positive end-expiratory pressure (PEEP) and on the peak airway pressure (PAP)[8–13]. Barotrauma produces clinical conditions such as pneumothorax caused by alveolar air leaks, pneumatocele, pneumomediastinum and subcutaneous emphysema. Treatment of these complications usually consists of a chest drain; collar mediastinotomy occasionally becomes necessary. In some patients, however, long-term artificial ventilation with high pressure causes such damage in the lung that these limited procedures may be insufficient and more extensive surgery is indicated. Experience in this situation is minimal and these patients are often so critically ill that they might be judged unsuitable for further surgery.

The use of $ECCO_2$-R in Marburg since 1985 has led to a unique experience with this new technology and to an increased

Table 1 *Respiratory failure classification according to Morel* et al.[2]

Stage	Chest radiology	$P_{Aa,O_2}/Fi_{O_2}$* (mmHg)	C_{rs} (ml/cmH_2O)	P_{pa} (mmHg)
0	Normal	< 300	> 80	< 20
1	Moderately increased interstitial marking	300–375	70–80	20–25
2	Markedly increased interstitial marking	375–450	50–70	25–30
3	Patchy air-space consolidation	450–525	30–50	30–35
4	Extensive air-space consolidation	> 525	< 30	> 35

$P_{Aa,O_2}/Fi_{O_2}$, alveolar/arterial oxygen tension difference divided by fraction inspired oxygen; C_{rs}, static compliance of the respiratory system; P_{pa}, mean pulmonary arterial pressure; * continuous positive pressure ventilation with peak airway pressure or positive end-expiratory pressure > 5 cmH_2O increases this particular score

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incidence of surgery in critically ill patients with severe manifestations of barotrauma and other lung complications. Such problems are seen in many patients on long-term artificial ventilation, but their severity is greater in those who require $ECCO_2$-R. The nature of this surgery is new and different from general thoracic surgery because: (1) the lung is diffusely changed and is severely damaged by artificial ventilation and inflammation; and (2) respiratory therapy has to be continued after operation despite the fact that this was the very reason for the operation in the first place.

Patients and methods

Seventy-six patients with ARDS stage 4 (Morel classification)[2] were treated with $ECCO_2$-R between July 1985 and December 1989. Seventy-four of the patients had been transferred from other hospitals. Before $ECCO_2$-R was instituted all other possible conventional ventilation therapy had been tried. All patients had a tracheostomy. Respiratory therapy under $ECCO_2$-R was performed by means of a Servoventilator 900 C (Siemens Company, Munich, FRG) and three or four intermittent mandatory ventilation breaths. PAP ranged between 35 and 40 cmH_2O and the maximum PEEP level was between 25 and 35 cmH_2O. Carbon dioxide removal occurred over a membrane lung situated in a bypass from the femoral vein to the inferior vena cava.

As soon as pulmonary problems had improved, $ECCO_2$-R treatment was discontinued to be followed by conventional artificial ventilation from which patients were eventually weaned over the ensuing days. A significant respiratory improvement was obvious when test ventilation with pure oxygen and an arterial oxygen tension of at least 400 mmHg was reached using a PEEP of 10–14 cmH_2O under normal tidal volume and respiratory rate (comparable with stage 2 of the Morel classification). The patients were divided into two groups:

(1) Group 1 consisted of 50 patients (66 per cent) who did not require thoracic surgery. These patients had no indication for operations like those mentioned in group 2, although the general condition of the patients did not preclude surgery, if indicated.

(2) Group 2 consisted of 26 patients (34 per cent) in whom thoracotomy became necessary (excluding 'minithoracotomies'). In all 26 patients a thoracic drain was inserted before operation, mostly because of pneumothoraces. Indications for operation were persisting high output parenchymal air leaks (more than 2 l/min or more than 25 per cent of tidal volume); large and mostly lobulated pneumothoraces or pneumatoceles causing major compression of the lung parenchyma, visible by computed tomography scanning; infected lung necrosis with concomitant fistula or sepsis; major bleeding with haemothorax; and persisting oesophagotracheal fistula.

Table 2 shows the primary diseases causing ARDS in group 2 patients; clinical data are summarized in *Table 3*. The 19 patients with barotrauma are listed separately.

Results

Fifty-one operations were carried out in group 2 patients. Forty-nine were done before or after $ECCO_2$-R and two were done during extracorporeal support with non-coagulation due to high-dose heparin therapy. The operations were divided into 35 primary operations and 16 reoperations (*Tables 4* and *5*). The most frequent indications for primary operation and reoperation were manifestations of barotrauma, specifically high output from persisting alveolar air leaks or loculated tension pneumothoraces insufficiently treated by drainage. Seven patients had a total of 13 thoracotomies because of complications not caused by barotrauma.

Table 2 *Primary disease of 26 patients who underwent thoracotomy*

Primary disease	No. of patients	No. of patients with barotrauma
Multiple injuries	16	11
Pneumonia	6	4
Sepsis after operation	3	3
Inhalation trauma	1	1
Total	26	19

Table 3 *Clinical data of 26 patients who underwent thoracotomy*

	No. of patients	No. of patients with barotrauma
Age (years)		
Range	6–45	6–44
Median	25	25
Male/female	12/14	5/14
Artificial ventilation (days)		
Range	6–92	6–92
Median	49	31
Length of $ECCO_2$-R treatment (days)		
Range	3–24	3–23
Median	14	12

$ECCO_2$-R, extracorporeal carbon dioxide removal

Table 4 *Primary operations*

Indication	No. of patients	No. of operations
Barotrauma		
Bilateral air leaks/pneumothorax	9	18
Unilateral air leaks/pneumothorax	8	8
Pneumatocele	2	2
Independent of barotrauma		
Infected lung necrosis	4	4
Haemothorax	2	2
Oesophagotracheal fistula	1	1
Total	26	35

Table 5 *Reoperations*

Indication	No. of patients	No. of reoperations
Barotrauma		
Air leaks/pneumothorax	5	10
Independent of barotrauma		
Pneumonia and abscess	3	3
Postoperative bleeding	2	3
Total	10	16

Sixteen (62 per cent) of 26 patients in group 2 survived, including 13 of 19 patients with barotrauma. Among the eight patients who had only one thoracotomy on one side, there were five survivors, and among the 18 patients who underwent a bilateral thoracotomy or multiple unilateral thoracotomies, there were 11 survivors. In the ten patients who died, the cause of death was multiple organ failure caused by hypoxaemia (six patients), severe bleeding in both lungs (one patient), intracerebral bleeding (one patient), sepsis (one patient), and haemolytic uraemic syndrome (one patient). In group 1 there were 22 (44 per cent) survivors. All 28 patients in this non-operated group who died had an autopsy and none of them showed findings that, retrospectively, would have given any indication for thoracotomy.

Discussion

Barotrauma of the lung as a complication of artificial ventilation was first described in 1912 when Woolsey reported two patients who developed pneumothoraces after endotracheal intubation and ventilation[13]. In 1939 Macklin gave an adequate explanation for the pathophysiology of barotrauma[14] and demonstrated in cats that air can rupture overdistended alveolar walls and dissect along the perivascular or interstitial spaces.

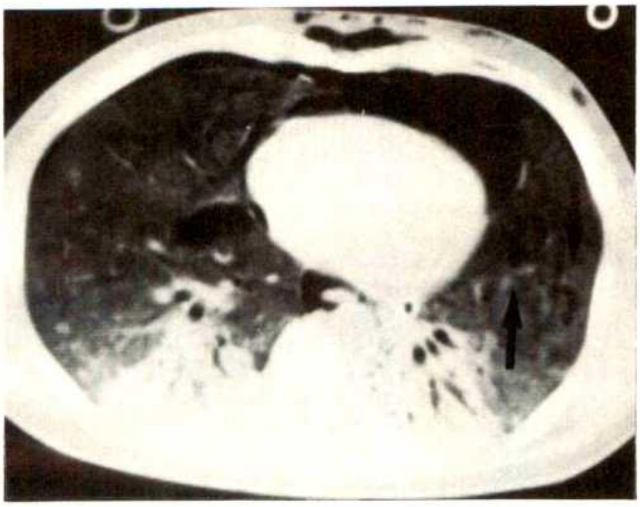

Figure 1 *Computed tomography scan showing pulmonary interstitial emphysema (arrowed), ventral pneumothoraces on both sides, and emphysema of the mediastinum and the thoracic wall*

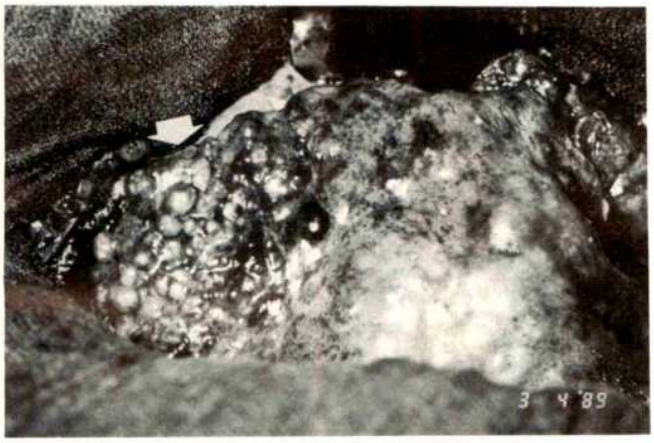

Figure 2 *Multiple subpleural emphysema bubbles in the lingula (arrowed)*

In ARDS the likelihood of barotrauma is increased by an unequal distribution of respiratory pressure in the lung. Ventilated areas close to areas of atelectasis are overdistended and normal alveolar architecture is obliterated[15].

Air in the interstitium is called pulmonary interstitial emphysema (*Figure 1*)[2,6,16,17]. This air may extend to the visceral pleura and then appear as subpleural interstitial emphysema bubbles on the surface of the lung (*Figure 2*). With continued mechanical ventilation these emphysema bubbles may rupture into the pleural cavity to form parenchymal leaks. Because of the high pressure of ventilation these leaks may cause a tension pneumothorax. Air from interstitial spaces may also dissect to the mediastinum and to the skin resulting in pneumomediastinum or subcutaneous emphysema. Pneumoretroperitoneum and pneumoperitoneum are less frequent complications. Air in the lung interstitium may form a bubble measuring several centimetres in diameter to produce a pneumatocele (*Figure 3*).

Pneumothoraces caused by alveolar air leaks are the most frequent manifestations of barotrauma and often appear on both sides. Incidences of pneumothorax in ARDS stage 4 range from 70 to 80 per cent[11]. This complication is not specific for patients undergoing $ECCO_2$-R and may occur in any mechanically ventilated patient. It is normally sufficient to decompress the pleural cavity with a chest drain. In a patient on long-term mechanical ventilation, chest drainage should not be done using a tube with a trocar in the lumen; a so-called minithoracotomy is more appropriate. If the drainage position is correct the lung should re-expand. In the authors' experience, surgical treatment of air leaks in these patients is less often required than in general thoracic surgery. With a spontaneously breathing patient, the persistence of parenchymal leaks over an interval of approximately 2 weeks is an indication for operation. With a mechanically ventilated patient, however, the volume of the air leak is much more important.

If the volume of the pneumothorax is so large that it jeopardizes artificial respiration or weaning from the respirator, thoracotomy is necessary. In contrast, it is the authors' experience that fistulae of small volume tend to seal spontaneously, even after several weeks, as soon as the airway pressure is reduced. In such cases thoracotomy is not necessary. A further indication for operation is unilateral multiple lobulated pneumothoraces, with no connection to each other, which cannot be drained sufficiently by percutaneous means (*Figure 4*) and which cause significant lung compression visible on computed tomography scanning.

Surgery starts with the dissection of pleural adhesions that are often seen in ARDS and which develop between the visceral and parietal pleura to such an extent that the lung cannot be distended completely. Large fistula outlets are then oversewn with absorbable monofilament suture. Small air leaks are not sutured since the needle may create further leaks which simply exacerbate the problem.

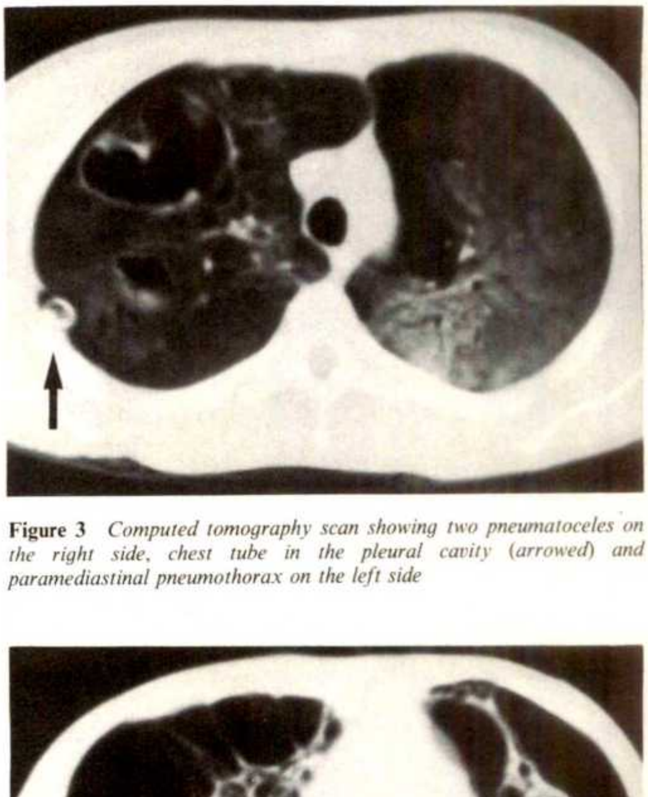

Figure 3 *Computed tomography scan showing two pneumatoceles on the right side, chest tube in the pleural cavity (arrowed) and paramediastinal pneumothorax on the left side*

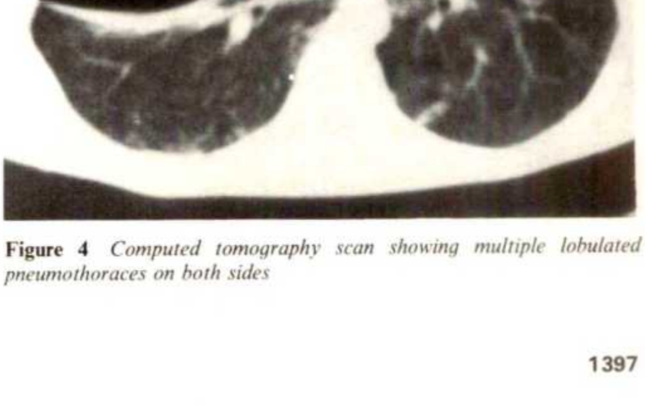

Figure 4 *Computed tomography scan showing multiple lobulated pneumothoraces on both sides*

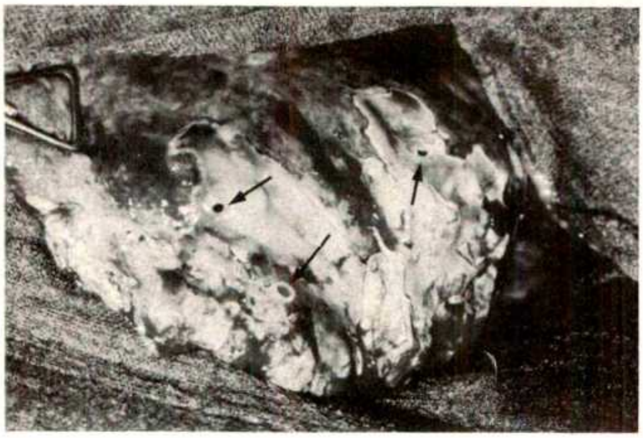

Figure 5 *Infected lung parenchyma with necrosis of the left upper lung lobe with multiple significant bronchopleural fistulae (arrowed)*

Pulmonary resection in this clinic was carried out only if there was pulmonary necrosis. Every effort must be made to preserve as much pulmonary parenchyma as possible because even severe interstitial and alveolar damage may resolve after ARDS[18]. In addition, if resection is carried out, the continued necessary high airway pressure will place tension on a new suture line, risking further large fistulation. Fibrin glue is not useful in this situation because it fails to remain adherent. The primary objective of such surgery is to reduce the output from leaks to such an extent that ventilatory support is not affected. The number of reoperations needed to achieve these goals may be high.

Alveolar air leaks may lead to mediastinal emphysema which may cause compression of the heart and/or the large vessels and require a collar mediastinotomy. Long-term artificially ventilated patients do not usually require such an operation, because they normally have a tracheotomy which decompresses the mediastinal emphysema. Air leaks may also lead to vast subcutaneous emphysema.

Pneumatocele, another manifestation of the barotrauma, may compress the surrounding lung parenchyma. Seriously compromised ventilation is an indication for operation. Surgical management in these cases consists of a wedge resection or opening the pneumatocele transpleurally with suturing of bigger fistulae.

Complications unrelated to barotrauma which require urgent thoracotomy are relatively rare in long-term artificially ventilated patients. In the present series infected parenchyma, necrosis as a consequence of lung contusion, haematoma and abscess predominated. These complications must be treated surgically because they are potential sources of sepsis or high output fistulae (*Figure 5*). The procedure of choice is resection and closure with a stapling device. Anatomical lobectomy is rarely necessary.

Haemothorax is a further possible complication. Bleeding may be from a vessel of the thoracic wall, especially after the insertion of a chest drain. The use of high-dose heparin, as required for $ECCO_2$-R treatment, may cause diffuse bleeding. This is why heparin-bound tubes have been used here since June 1988. In two patients bleeding enforced an early discontinuation of the therapy. Lesions of the lung parenchyma may also lead to haemothorax. In this series the indication for operation was a continuous blood loss of 300–500 ml/h over a period of 3 h or, more often, persistent oozing with accumulation of blood in the pleural cavity, compressing the lung.

An oesophagotracheal fistula is a rare complication during long-term respiratory therapy; it is caused by local pressure necrosis from the cuff of the endotracheal tube. In persisting fistulae, operation is necessary. The fistula should be closed by sutures which are covered by a muscle or pleura flap.

The most striking finding in the present series of patients was that there were more survivors in the group of operated patients than in the group not requiring surgery. Both groups were comparable with regard to ARDS stage 4, which was exacerbated by complications linked to surgery in the group of patients with thoracotomies. No patient was excluded from surgery because of their critical state. The autopsy findings proved that there had been no indication for thoracotomy in any of the deceased patients who were not operated on. The higher survival chances of patients undergoing surgery may be coincidental. A possible explanation may be that the degree of fibrosis or disease within the lungs of patients who do not develop surgical complications is such that this is less compatible with survival. The fact remains, however, that barotrauma, with or without extracorporeal support, in patients on long-term artificial ventilation must be treated surgically when indications arise. Thoracotomy and re-exploration does not appear to diminish the survival chance of these high-risk patients with severe ARDS.

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For debate

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Outcome measurement using hospital activity data: deaths after surgical procedures

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There is a pressing need to develop measures of health outcome for use in medical audit and in shaping decisions on the allocation of resources. Such measurement is not normally performed except in specific research settings. Routine information collected on hospital inpatients contains very crude data on two health outcomes, namely whether such patients were alive or dead at the end of their hospital stay. This paper analyses hospital activity data with particular reference to those patients who had undergone a surgical procedure. The results are broadly consistent with the earlier findings of the Confidential Enquiry into Perioperative Deaths and reveal a crude mortality rate of under 15 deaths per 1000 surgical admissions. Rates as high as 280 per 1000 admissions were found for certain procedures. Since death is a relatively rare health outcome it is argued that the development of a more acceptable measure must be a priority to provide information on the vast majority of surgical patients with non-fatal outcomes.

Keywords: Health outcomes, mortality, hospital activity analysis

In 1987 the report of the Confidential Enquiry into Perioperative Deaths[1] documented a detailed examination of deaths in three regional health authorities. The foreword to the report reflected the growing interest in quality assurance in medical care and called for peer review of clinical practice. Such reviews must consider the outcome of health care as well as the process of its delivery, a theme endorsed in the recent White Paper[2]. The process of audit requires detailed information on individual patients, their investigation, diagnosis and treatment. These data are more easily obtained than systematic information on health outcomes which are characteristically absent. Indeed this point was made recently by the Chief Medical Officer in his report[3] which emphasized the need for 'more and better measures of the outcome of the activity of the National Health Service, with particular respect to reduced premature mortality and improved quality of life'.

Monitoring and review of this type, however, depends upon the availability of relevant information concerning both the local experiences and the wider, national picture. A large volume of potentially useful data is recorded within hospital activity analysis (HAA), until recently the principal patient information system. *Inter alia*, HAA recorded the patient's entry to, and exit from, hospital. A patient's 'disposal' at the end of a hospital stay is classified in four ways: transfer to another hospital, discharge home, sent for convalescence or death. This classification may be reduced to a simpler, albeit somewhat crude, classification of health outcomes: patients leave hospital alive or dead. Various mortality rates may be calculated using such a classification, and an analysis of standardized mortality rates for 192 health authorities has already been published[4]. This paper reports on the analysis of outcomes in the subset of the patient population who had a surgical procedure performed upon them during their hospital stay.

Patients and methods

HAA contained information on over five million hospital episodes relating to patient admissions in the 14 English regional health authorities. The full HAA dataset provided the source data for the one in ten sample on which the Hospital Inpatient Enquiry (HIPE) reports are based. A copy of the HIPE data for 1985 was obtained from the Office of Population Censuses and Surveys (OPCS) and forms the basis of the analysis presented here.

Each patient record is made up of fixed data-items including the four-digit OPCS code which categorizes any operation or other surgical procedure that the patient may have undergone. For the purposes of this paper patients were categorized as 'surgical' cases if their HIPE record contained an OPCS operation code indicating that they had undergone a surgical procedure during their hospital stay. The terminology of the OPCS classification used to describe operations and procedures has been reproduced throughout this paper.

Results

Table 1 shows the ten specialties which account for 90 per cent of all operations and surgical procedures. The death rate is highest in neurosurgery with 61 deaths per 1000 admissions, twice that for general surgical patients. Nearly one in three of

Table 1 *Specialties in which the majority of patients undergo surgery*

Principal surgical specialties	Number of patients in HIPE sample	Percentage receiving surgery	Death rate per 1000 surgical admissions
General surgery	96 372	65·2	31
Gynaecology	56 666	81·1	3
Trauma and orthopaedics	51 202	65·5	19
Ear, nose and throat	26 908	82·9	4
Urology	14 900	73·5	19
Ophthalmology	13 388	76·7	1
Dental surgery	8 891	88·5	1
Plastic surgery	5 365	83·7	6
Thoracic surgery	3 752	73·3	43
Neurosurgery	2 850	61·2	61
All specialties	498 695	45·4	15

HIPE, Hospital Inpatient Enquiry

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all patients admitted to both specialties did not undergo surgery during their hospitalization. The crude death rate amongst all patients who had surgery is 15 per 1000 admissions.

Overall there is a lower death rate amongst surgical patients than the 5·5 per cent previously reported for the general hospital population[4]. At a regional level, death rates vary from 11 to 20 per 1000 surgical admissions. The small numbers of deaths recorded for certain procedures make it difficult to draw comparison between all regions. Thoracic surgery has one of the higher death rates with a twofold variation between the highest and the lowest. Overall, however, the range of death rates for each operation group is similar across the regions.

Although sample size restricted more detailed comparisons it was possible to examine death rates for selected groups of surgical procedures. Some operations are performed more frequently than others. Procedures were classified as high activity if there were more than 2000 in the HIPE sample (equivalent to 20 000 such operations a year in the 14 English regions). Death rates for these operations are given in *Table 2*. For the majority of these the death rate is virtually nil, the sole exception being laparotomy with a mortality rate of 142 per 1000 surgical cases. Judged in the context of the general surgical rate the figures for gastric intubation (39 per 1000) and reduction with internal fixation (59 per 1000) are also noteworthy. The death rate associated with a laparotomy varies considerably according to the patient's diagnosis. *Table 3* gives the principal diagnoses recorded for patients undergoing laparotomy. More than 70 per cent are performed on patients with malignant neoplasms, diseases of the digestive system, and women with genitourinary disorders. Death rates vary from 17 per 1000 for non-inflammatory disorders of the ovary to 377 per 1000 for malignant neoplasm of the pancreas, a figure some 22 times higher, reflecting the biological nature of the disease.

A second group of surgical procedures was identified as having a high death rate if there were more than 100 cases reported in the HIPE sample and the death rate exceeded 10 per cent. These procedures are listed in *Table 4*. The highest rates are for arteriotomy (284 per 1000) and amputation through thigh (261 per 1000).

The proportion of deaths in the HIPE sample for which a post mortem is recorded varies considerably according to health authority and admitting specialty, as can be seen in *Table 5*. Post-mortem rates vary across the regions from 12 to 36 per 100 surgical deaths, and there is a sixfold variation between specialties within region. The post mortems for patients in trauma and orthopaedics run at higher absolute rates than for other specialties, perhaps because of the need to establish cause of death for other purposes or agencies.

The crude surgical death rates were calculated for each of the 192 health authorities and are shown graphically in *Figure 1**. The death rates vary from less than four per 1000 admissions (an authority in South-West Thames Regional Health Authority) to over 40 per 1000 (an authority in West Midlands Regional Health Authority). These rates are of course highly sensitive to errors in coding and/or completeness. Comparison with previously published tables of standardized mortality rates[4] reveals that three authorities have both relatively high surgical death rates and high standardized mortality rates for the sampled hospital population. Only one authority has correspondingly low rates on both indices. Interpretation of such mortality data needs great care and is best conducted by those with an intimate knowledge of local circumstances.

Mortality rates computed for individual health authorities may be affected by various factors such as age, case-mix and level of surgical activity. To gauge the impact of age on mortality rates patients were assigned to one of three age bands: under 45 years, 45–65 years and over 65 years. *Table 6* shows the extent to which the crude death rate for the three procedures

Table 2 *Specific high activity operations and procedures*

OPCS code	Surgical procedure	No. of cases	No. of deaths	Death rate per 1000 admissions
28	Spinal puncture	2029	14	7
174	Intracapsular extraction of cataract	2547	2	<1
193	Myringotomy and tympanostomy	3522	0	0
233	Tonsillectomy with adenoidectomy, not classified elsewhere	2930	0	0
234	Other tonsillectomy	2012	0	0
252	Surgical extraction of tooth	4919	1	<1
381	Partial mastectomy	2685	3	1
401	Paracentesis abdomini	3618	25	7
402	Laparotomy	2278	324	142
411	Repair of inguinal hernia, not classified elsewhere	6378	18	3
431	Gastric intubation with related procedures	4534	176	39
441	Emergency appendicectomy	3429	8	2
468	Sigmoidoscopy	2988	37	12
522	Cholecystectomy	3136	37	12
607	Cystoscopy with bladder lesion destruction	2026	19	9
608	Cystoscopy, not classified elsewhere	6445	45	7
633	Prostatectomy, per urethral	3053	32	10
661	Circumcision	2187	1	<1
687	Bilateral endoscopic occlusion of oviducts	2371	0	0
696	Hysterectomy, not classified elsewhere	3380	3	1
704	Curettage of uterus	10 133	3	<1
742	Other termination of pregnancy	4563	0	0
771	Other removal of products	6233	0	0
780	Manipulation of closed fracture	3378	15	4
782	Reduction with internal fixation	4643	273	59
801	Joint puncture	2508	5	2
810	Total hip replacement	2447	51	21
894	Varicose veins, not classified elsewhere	2313	1	<1

OPCS, Office of Population Censuses and Surveys

Table 3 *Principal diagnoses associated with laparotomy*

ICD code	Diagnosis	No. of cases	No. of deaths	Crude death rate per 1000 admissions
140–209	All malignant neoplasms	666 (29)	176	264
520–579	All diseases of the digestive system	690 (30)	91	132
614–629	Diseases of the female genitourinary system	281 (12)	2	7
780–799	Ill-defined conditions	209 (9)	4	19

Numbers in parentheses are the percentages of all laparotomies performed; ICD, International Classification of Diseases

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* *A full listing of of crude surgical death rates for each of the 192 English health authorities is available from the author.*

Table 4 *Specific surgical procedures with high mortality rates*

OPCS code	Surgical procedure	No. of cases	No. of deaths	Death rate per 1000 admissions
53	Evacuation of haematoma or cyst	110	16	146
422	Gastrectomy, total or radical	139	24	173
423	Partial gastrectomy	371	47	127
426	Gastroenterostomy	162	28	173
427	Repair of stomach	102	16	157
452	Excision of small intestine or lesion	124	19	153
454	Anastomosis of intestine, not classified elsewhere	108	16	148
458	Repair of perforated duodenal ulcer	148	22	149
462	Colostomy, primary	279	52	186
552	Operation on abdominal vessels, not classified elsewhere	377	79	210
811	Other arthroplasty of hip	1221	127	104
871	Amputation through thigh	307	80	261
873	Amputation through lower leg	203	24	118
880	Arteriotomy	201	57	284
967	Resuscitation by external procedures	117	22	188

OPCS, Office of Population Censuses and Surveys

most commonly associated with a fatal outcome changes with increasing age. Older patients undergoing surgery are some 15–20 times more likely to die than younger patients having the identical procedure. In addition, there is an increase in the length of stay, with an effective doubling in duration for the older surgical patients.

A significant negative correlation was found between surgical death rates and the surgical workload expressed as a proportion of the total patient throughput (Pearson's $r = -0{\cdot}2744$, $P < 0{\cdot}001$). The average surgical workload is 45 per cent of hospital throughput, with eight health authorities recording a surgical workload of more than 60 per cent. Hospitals with a greater proportion of surgical cases had a correspondingly lower surgical mortality rate. Surgical death rates do not vary significantly with hospital size as measured

Table 5 *Variation in post-mortem rates for selected specialties (rates per 1000 deaths)*

Regional Health Authority	General medicine	General surgery	Trauma and orthopaedics	All surgical patients
Northern	8·3	23·7	27·3	221
Yorkshire	14·3	14·6	41·9	183
Trent	24·4	29·4	50·9	299
East Anglia	14·8	5·2	65·0	228
North-West Thames	18·2	12·1	50·0	218
North-East Thames	26·1	16·3	16·4	211
South-East Thames	22·4	35·7	54·9	336
South-West Thames	14·9	20·6	60·0	303
Wessex	16·7	22·6	36·1	243
Oxford	13·5	16·0	36·8	157
South Western	18·2	23·8	48·3	293
West Midlands	23·5	32·6	39·6	319
Mersey	4·2	14·5	22·7	123
North Western	33·3	29·1	59·2	364

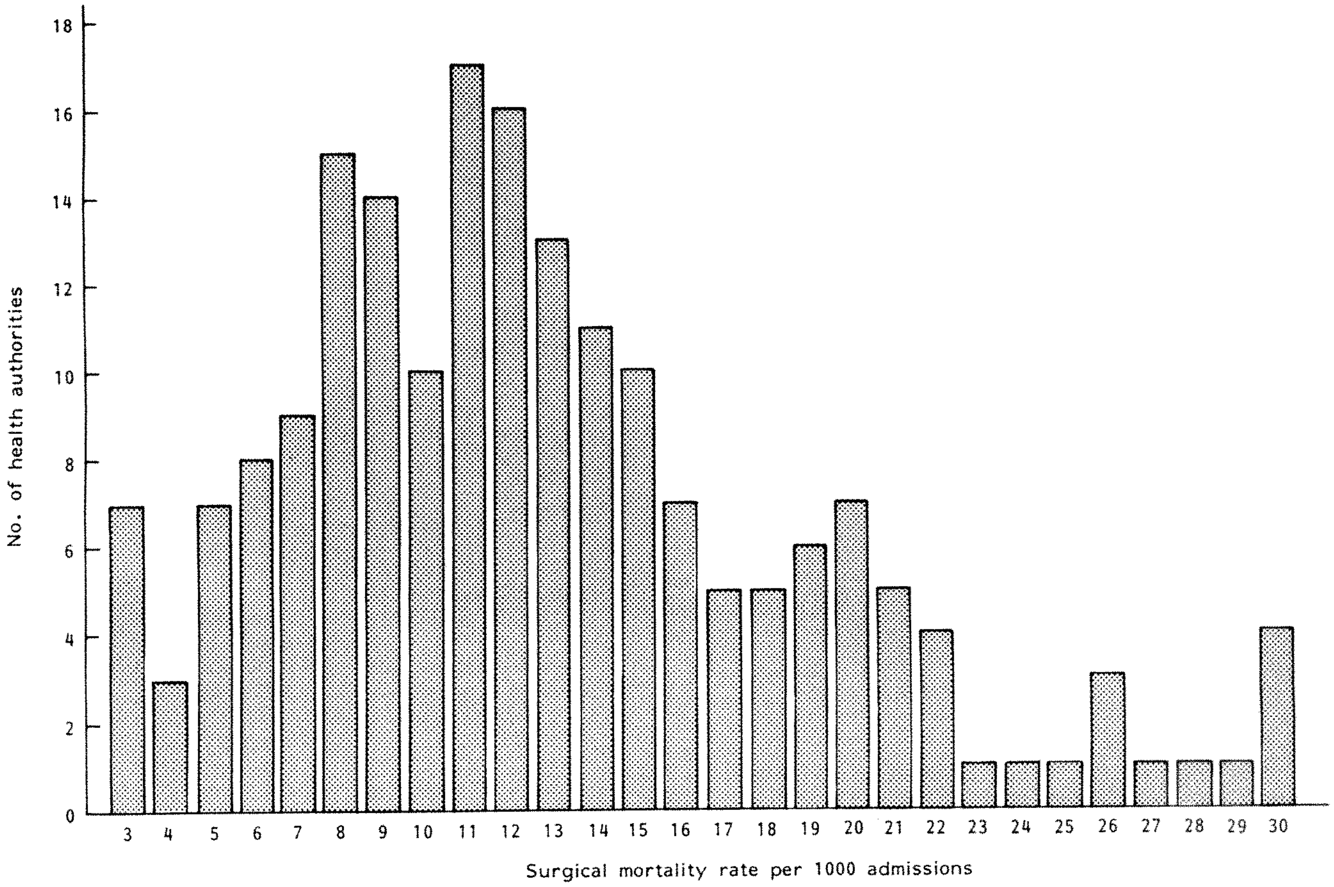

Figure 1 *Distribution of crude surgical mortality rates in 192 health authorities*

Table 6 *The impact of age on length of stay and death rates for three surgical procedures*

Surgical procedure (OPCS operation code)	Age range of patient (years)	Mean length of stay (days)	Crude death rate per 1000 admissions
Laparotomy (402)	Under 45	10·8	15
	46–65	18·2	120
	Over 65	19·2	285
Reduction with internal fixation (782)	Under 45	11·8	<1
	46–65	16·2	14
	Over 65	29·4	116
Gastric intubation with related procedures (431)	Under 45	4·5	4
	46–65	6·9	23
	Over 65	10·6	66
All surgical procedures	Under 45	4·2	1
	46–65	6·9	9
	Over 65	10·5	31

OPCS, Office of Population Censuses and Surveys

in terms of total throughput, despite the slightly higher mean age of patients in smaller hospitals. Mean length of stay remained constant for surgical patients in all three groups of hospital.

Discussion

Mortality data provide incomplete information on health outcomes. For patients who undergo surgery the death rate is less than 15 per 1000 admissions. Thus for the vast majority of patients who undergo surgery no outcome data are recorded beyond the fact of their survival. Even amongst the relatively small number of patients who die it is difficult to link that outcome with any specific intervention. Death may have resulted from causes altogether unconnected with surgery. A binary classification (alive/dead) is unlikely to be useful, except for those high activity procedures which also happen to have high death rates.

The variation in crude death rates between regions is very small and, although somewhat higher than the rates reported by the Confidential Enquiry into Perioperative Deaths, is well below that for the general hospital population. The Confidential Enquiry found considerable variations in rates linked to specific procedures: 20 per cent for aortic aneurysm repair and 0·04 per cent for appendicectomy. The corresponding death rates in this study are equally widely dispersed: 20 per cent and 0·23 per cent respectively. Commonly performed surgical procedures, with one exception, are associated with low mortality rates. The high rate reported for laparotomy probably reflects a shortcoming in the way that operations are coded. No distinction is made between emergency and elective procedures, or the reasons for operating. Furthermore, there is some doubt about the appropriateness of the coding system because some procedures listed in the OPCS classification are medical or diagnostic, rather than surgical. Surgeons may wish to question the usefulness of a classification that does not distinguish adequately between types of procedure or site of operation. Similar difficulties have been reported with the diagnostically related groups system, for example in aggregating radical and simple mastectomies[5].

The calculation of surgical mortality rate is susceptible to many factors, including errors and omissions in the recorded data. Low activity levels may also contribute to apparently high computed rates. However, it is unlikely that the 12-fold variation in mortality rates across health authorities reported here is wholly attributable to the variable quality of the data. Variations in mortality rate have been linked with degree of surgical specialization and experience[6]. On the basis of the data used in this study there is a significant relationship with the surgical workload. This could pose serious problems at a time when hospitals are being urged to consider opting out. If there is a causal link between volume and surgical mortality rate then it might be that some low activity procedures would be diverted to hospitals that offered better prospects for good surgical outcomes.

Despite obvious disadvantages mortality rates based on nationally collated data offer important information. For many surgical procedures there is an extremely low death rate which, when combined with a low activity rate, means that some surgeons will rarely, if ever, encounter a fatality. For some conditions or procedures even a single patient death may be regarded as wholly unusual and a cause for concern. Continual monitoring of mortality rates over time will provide essential baseline data.

The information needs of surgeons have to be weighed against the needs of other key decision-makers who might be satisfied with less sophisticated measures. Resource management systems offer surgeons the prospect of specifying their own local outcome classifications. This could lead to a proliferation of measures based on different criteria from which it would be nigh on impossible to derive any consensus regarding the impact of surgical care. Such a move should be resisted. It is essential to collate outcome data centrally from individual hospitals and health authorities, and this in turn dictates the use of a common standard.

There is a clear need for outcome measurement in hospitals to provide essential intelligence on the impact of treatments, and to generate information that can improve the quality of clinical decision-making. There are two practical requirements for its implementation. Firstly, some agreed standard classification of patient health status is needed which describes a variety of non-fatal states. A classification need not be too extensive to obtain a significant advance over our present capacity which describes patients only as alive or dead. Secondly, the measurement of patient health status at the end of a hospital episode, or after other interventions, has to be related to data on previous measurements taken on admission, or before treatment. Without these initial data, outcomes will continue to be defined in terms of clinical milestones or other variables considered indicative of change.

This paper has demonstrated the limited potential for using mortality data in the measurement of health outcomes. Such measurement is a basic requirement in evaluating the impact of treatments in individuals and groups of patients. In the long run this information could be based on a standard system of health status measurement. For the time being, in the absence of a more sophisticated technology, we may have to be satisfied with the blunt instrumentation which has been described here.

Acknowledgements

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Case report

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Fallibility of gastrin level as an indicator of complete excision of a gastrinoma

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The Zollinger–Ellison syndrome is characterized by peptic ulcer disease, high basal gastric acid secretion and raised serum gastrin values. Gastrin stimulation tests are frequently necessary in patients with moderately elevated serum gastrin levels to differentiate other hyperchlorhydric hypergastrinaemic states. The most sensitive and specific test is the secretin injection test[1–3]. It has recently been reported that bombesin, a 14-amino acid peptide, is also a potent gastrin secretagogue from gastrinomas[4]. Although peptic ulcer disease in the Zollinger–Ellison syndrome can be controlled by H_2-receptor antagonists or omeprazole, it is usual to resect the tumour because of its malignant potential. If tumour resection is complete, gastric acid secretion, basal and secretin-stimulated serum gastrin levels usually return to normal[1,5–7].

Relatively long periods of follow-up after operation may be necessary, however, to rule out residual tumour because the clinical course may be protracted. Repeated basal and secretin-stimulated serum gastrin levels are required to detect growth of residual tumour at an early stage. We describe a patient with Zollinger–Ellison syndrome in whom an apparently curative tumour resection was performed. A normal basal serum gastrin level after operation and a negative serum gastrin response to secretin injection proved no guarantee of complete tumour resection.

Case report

In November 1981 a 53-year-old man was admitted with a tentative diagnosis of Zollinger–Ellison syndrome. Since 1969 he had had recurrent duodenal ulcers and in 1979 cimetidine therapy was instituted. Because of resistant ulcer disease parietal cell vagotomy had been performed 5 months before admission. No tumour was identified at that time. After operation, complaints of epigastric pain, reflux and heartburn persisted, and basal acid output (BAO) remained elevated (36 *versus* 26 mmol/h before vagotomy). The fasting serum gastrin was increased to 230 pg/ml (*Figure 1*; normal value 10–70 pg/ml (Reference 8)). Duodenal ulcer recurrence was diagnosed endoscopically. A secretin test (1 clinical unit/kg secretin GIH, Karolinska Institute, Stockholm, Sweden) proved positive with a basal value of 150 pg/ml and a peak value after stimulation of 340 pg/ml (*Figure 2*). An abdominal computed tomography scan demonstrated an enlarged tail of the pancreas consistent with a tumour with enlarged regional lymph nodes. The liver and spleen were normal. Angiography revealed a hypervascular mass in the tail of the pancreas with possible invasion of the splenic vein. There was no evidence of multiple endocrine neoplasia type I and the family history was negative for this syndrome. Serum gastrin and calcium values in all children were normal.

A diagnosis of sporadic Zollinger–Ellison syndrome was made. In February 1982 a laparotomy was performed and distal pancreatectomy and splenectomy were carried out. Tumour invaded the splenic vein and was found in a lymph node in the transverse mesocolon. The proximal resection surface was free from tumour. The gastrin concentrations in the tumour were 2·1 ng/g tumour tissue.

Two days after operation the serum gastrin level decreased to a normal level of 42 pg/ml (*Figure 1*) and 6 weeks after surgery the secretin test was negative (*Figure 2*); the BAO value was in the normal range (2·1 mmol/h), suggesting curative tumour resection. In July 1982 the patient developed recurrent complaints of heartburn and dyspepsia. Barium meal and endoscopy showed no abnormalities. Six months after operation the serum gastrin level was slightly elevated (105 pg/ml; *Figure 1*) and 2 months later a computed tomography scan showed liver metastases. The patient was treated with cimetidine at doses of up to 1600 mg daily. The serum gastrin level rose enormously (*Figure 1*), but the secretin tests remained negative (*Figure 2*). A bolus injection of a higher dose of 3 clinical units/kg secretin GIH was also negative. However, infusion of bombesin (bombesin 14, Boehringer Mannheim Biochemicals, Indianapolis, Indiana, USA; 100 ng/kg over 20 min) gave a brisk and large rise of serum gastrin concentrations (*Figure 3*). Two years after surgery severe complaints of heartburn were poorly controlled by the high dose of cimetidine, and from March 1984 treatment with omeprazole, 60 mg daily, was instituted.

The patient became free from symptoms and the BAO level remained below 1 mmol/h. Computed tomography scanning showed progression of liver metastases (*Figure 4*) and liver function tests became abnormal. The patient deteriorated rapidly and died 46 months after surgery. Autopsy was not permitted.

Discussion

Resection of a gastrinoma is said to be complete if two conditions are fulfilled: (1) normal basal serum gastrin after operation and (2) a positive secretin injection test becomes negative.

These conditions were met in our patient but follow-up revealed evidence of early tumour recurrence. In view of the large pancreatic mass and positive nodes in the transverse mesocolon found at laparotomy, recurrence was not unexpected.

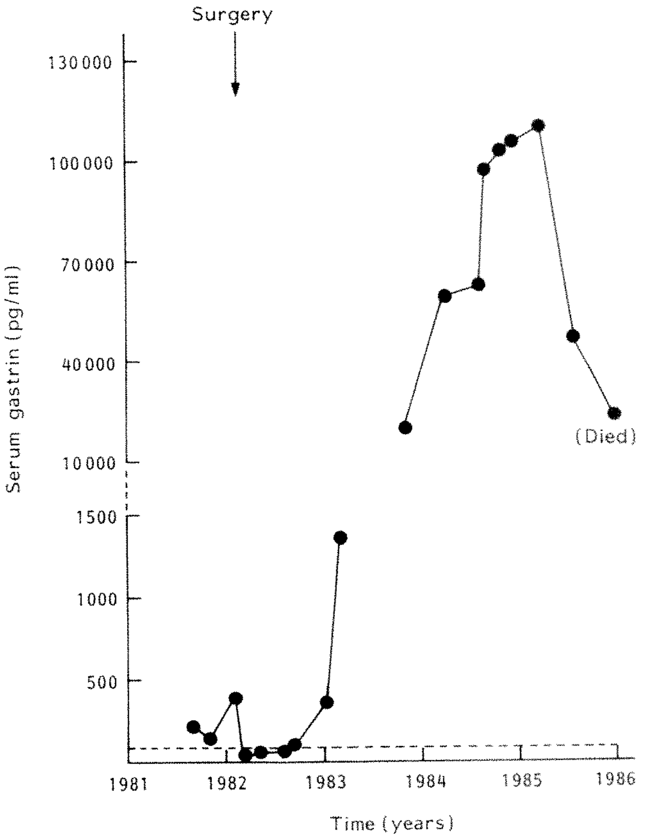

Figure 1 *Serum gastrin levels before and after tumour resection. The dotted line shows the upper limit of the normal range (70 pg/ml)*

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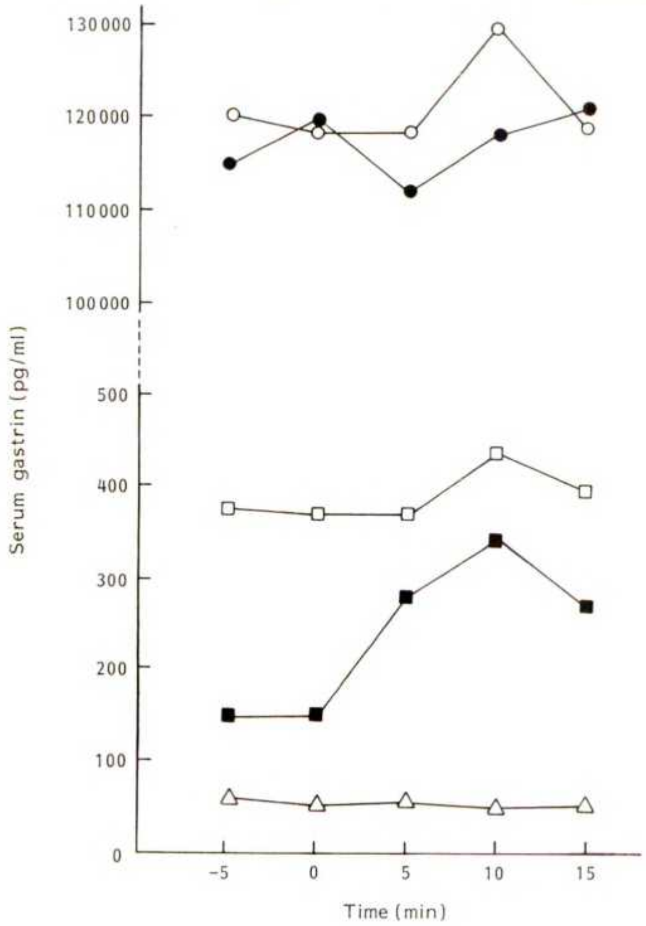

Figure 2 *Serum gastrin levels after a bolus intravenous injection of 1 clinical unit/kg secretin at time zero before and after tumour resection.* ○, *March 1985;* ●, *November 1985;* □, *December 1982;* ■, *November 1981;* △, *April 1982*

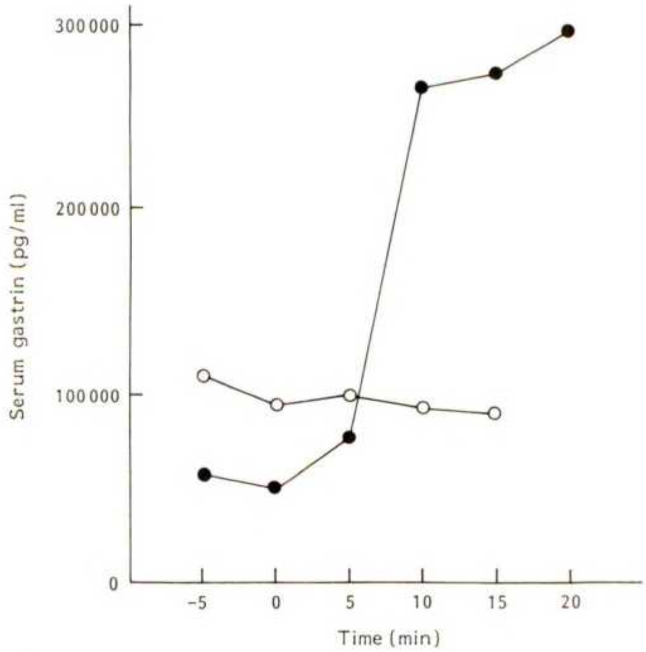

Figure 3 *Serum gastrin levels after a bolus intravenous injection of 3 CU/kg secretin,* ○, *at time zero and after infusion of 100 ng/kg bombesin,* ●, *over 20 min*

During follow-up basal gastrin levels correlated well with the progression of the disease. The development of a secondary primary tumour seems unlikely. The development of liver metastases was, perhaps, inevitable because invasion of the splenic vein was found at operation.

A few patients have been described with normal basal serum gastrin values after operation and a negative secretin injection test but they did not show clinical or laboratory signs of recurrence during a follow-up period varying from 1 to 60 months[1,5–7]. In our patient there was a steady increase in the basal serum gastrin value, yet the secretin test remained negative during all 4 years of follow-up.

This provocation test was also negative when a larger dose (3 clinical units/kg) of secretin was used. This confirms our previous finding that larger doses of secretin do not increase the sensitivity of the test[8,9]. Metastatic disease present in the liver at that time was either too small in volume to evince a rise on secretin stimulation or had altered receptors. The reason for the failure to respond to secretin after operation is not apparent. The possibility that the secretin test would become positive if the test had been preceded by calcium administration cannot be excluded[10]. McCarthy[11] found that in patients with extensive metastatic gastrinoma the response to secretin stimulation was frequently small.

Richardson *et al.*[7], however, found a positive correlation between the level of basal serum gastrin and the increases of gastrin after stimulation by secretin. Decrease in serum gastrin during the end-stage of the disease may have been caused by tumour necrosis. Others have shown no correlation between tumour bulk and serum gastrin value[12].

Infusion of bombesin resulted in a dramatic increase of serum gastrin, suggesting that bombesin stimulates the tumour by a different mechanism. Bombesin stimulation may be more sensitive than the secretin test in detecting recurrent gastrinoma in some patients with Zollinger–Ellison syndrome. Bombesin is capable of stimulating gastrin secretion from gastrinoma cells in culture indicating a direct action of this polypeptide on the tumour cells[13].

In conclusion, to our knowledge this is the first patient with Zollinger–Ellison syndrome in whom negative secretin-stimulated serum gastrin levels did not indicate curative tumour resection.

Acknowledgements

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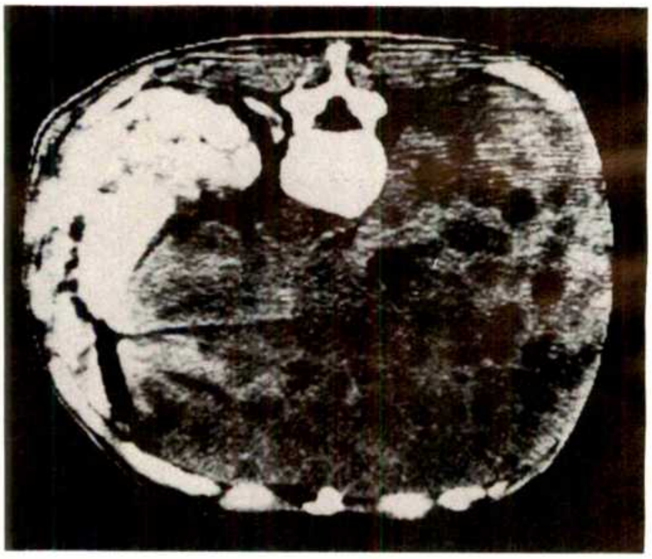

Figure 4 *Abdominal computed tomography scan: multiple metastases in the liver are shown*

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Announcement

Regular readers of *The British Journal of Surgery* will be aware that the pagination of the *Journal* has increased significantly every year since 1986. It is therefore inevitable that subscription prices for the *Journal* should increase; however, we would like to illustrate to our subscribers that they are receiving better value for money than ever before.

In 1987, each page of the *Journal* cost 3.90 pence for individual subscribers, 4.57 pence for UK institutions and 5.15 pence for overseas institutions (1204 pages in total). If these prices had increased in line with the Retail Prices Index, they would now stand at 5.00 pence, 5.85 pence and 6.60 pence, respectively. In fact, the price per page of the *Journal* in 1991 will be 3.74 pence for individuals, 5.54 pence for UK institutions, 5.80 pence for European institutions and 6.30 pence for overseas institutions.

As the number of pages in the 1991 volume of *The British Journal of Surgery* will be 1552 (an increase of eight pages per issue), these small differences in the price per page represent considerable 'savings' for the reader.

Those subscribers who receive their copy of the *Journal* at the preferential Society rate might be interested to note that, in 1987, the price per page of their *Journal* was 2.90 pence. The absolute cost has not risen at all in line with the Retail Prices Index and the price per page remains at 2.90 pence!

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Reproduced from SURGERY 1990;4:655-9

Early tracheostomy for primary airway management in the surgical critical care setting

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*During a 12-month period, 264 patients with multiple injuries who required mechanical ventilation were admitted to the surgical intensive care unit. One hundred twenty patients (46%) were disengaged from the ventilator, and 38 patients (14%) died. Of the remaining 106 patients (40%) 51 patients (group I) were to receive tracheostomy within 1 to 7 days, and 55 patients (group II) underwent late (8 or more days after admission) tracheostomy. Multiple variables in four categories (admission, operative, ventilatory, and outcome) were analyzed prospectively to define the impact that early tracheostomy had on duration of mechanical ventilation, intensive care stay, and hospital stay. Morbidity and mortality rates of the procedures were assessed. Early tracheostomy, in a homogeneous group of critically ill patients, is associated with a significant decrease in duration of mechanical ventilation, as well as shorter intensive care unit and hospital stays, compared with translaryngeal endotracheal intubation. There were no deaths attributable to tracheostomy, and overall morbidity of the procedures was 4%. We conclude that early tracheostomy has an overall risk equivalent to that of endotracheal intubation. Furthermore, early tracheostomy shortens days on the ventilator and intensive care unit and hospital days and should be considered for patients in the intensive care unit at risk for more than 7 days of intubation. (*SURGERY *1990;108:655-9.)*

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MECHANICAL VENTILATION REQUIRING cannulation of the trachea is an integral part of the therapy provided to patients in the surgical critical care setting. In the 1950s and early 1960s, airway management consisted of a short period of translaryngeal intubation quickly converted to tracheostomy. In the late 1960s and 1970s the time of translaryngeal intubation before tracheostomy gradually increased with the development of improved endotracheal tube design and construction. This concept became the standard of care in critical care units,[1-6] irrespective of the type of patient cared for. In the late 1970s and early 1980s Dane and King,[7] El Naggar et al.,[8] and Stauffer et al.[9] compared translaryngeal intubation with tracheostomy in critically ill patients. Outcome analyses centered solely on the complications of tracheostomy and risk of tracheal stenosis. These studies have frequently been cited to demonstrate the dangers of tracheostomy and the high incidence of morbidity and death as a result of the procedure and supported prolonged translaryngeal intubation to avoid tracheostomy until absolutely necessary. In several well-performed prospective studies,[10-12] the controversy concerning perioperative morbidity and death and timing of tracheostomy after translaryngeal intubation were addressed. These reports demonstrated that morbidity and mortality rates of tracheostomy were low and translaryngeal intubation of less than 7 days was associated with a risk of transient laryngeal injury of less than 10%. Tracheostomy after 7 days of translaryngeal intubation had a significant incidence of irreversible laryngeal and tracheal stenosis. On the other hand, in a prospective,

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Table I. Admission factors

Factor	*Group I*	*Group II*
Age (yr)	36 ± 2	39 ± 2
Sex (% male)	80	78
Type of Injury (% blunt)*	90	95
Injury Severity Score	28 ± 2	27 ± 1
Glasgow Coma Score	10 ± 1	10 ± 1
Hypotension (%)	35	47

*Blunt versus penetrating

Table II. Admissions factors

Factor	*Group I*	*Group II*
Cranial neurologic injury (%)	63	53
Chest injury (%)	39	40
Abdominal injury (%)	22	22
Extremity injury (%)	43	40
Fracture injury (%)	57	69
APACHE II score	10 ± 1	10 ± 1
Chronic illness (%)*	12	15

*Presence of preexisting cardiac or pulmonary disease

randomized study with a homogeneous patient population cared for in the surgical critical care setting, Dunham and La Monica[13] demonstrated that there were no significant differences in the incidence of complications between early and late tracheostomy.

Currently, tracheostomy plays a vital role in the care of many critically ill patients and has become one of the most common operations performed in the critical care unit. Yet few data are available defining the impact that timing of tracheostomy has on duration of mechanical ventilation or intensive care unit or hospital stay. Therefore this study was completed to compare, prospectively, results in an homogeneous group of patients with multiple injuries who underwent tracheostomy early (within 7 days) versus late (after 8 days) in a single surgical critical care unit.

PATIENTS AND METHODS

Patients with multiple injuries requiring mechanical ventilation were admitted to the surgical intensive care unit and consecutively allocated by the date of admission into one of two groups. Group I, odd-day admission, underwent tracheostomy within 7 days of admission to the intensive care unit. Group II, even-day admission, underwent tracheostomy later than 8 days of stay in the intensive care unit. Excluded were patients who did not require ventilator therapy for more than 1 day, patients who were being actively disengaged from the ventilator, and patients who died within the first 24 hours.

Table III. Operative factors

Factor	*Group I*	*Group II*
Operative procedure (%)	76	73
Anesthesia time (hr)	4 ± 0.4	3 ± 0.4
Incision location (%)		
Cranium	18	16
Thorax	8	5
Abdomen	25	22
Extremity	39	33
Fracture	52	60

Admission, operative, ventilatory, and outcome factors were compared between the two groups.

Admission. Factors evaluated included age, gender, type of injury (blunt versus penetrating) Injury Severity Score, Glasgow Coma Score, hypotension on admission (systolic pressure <90 mm Hg or clinical signs of shock), anatomic sites of injuries, presence of cranial neurologic injury (closed head injury with or without intracranial monitoring, epidural or subdural hematoma requiring evacuation, or craniotomy for removal of tissue), chest injury (three or more rib fractures, lung contusion, hemopneumothorax, flail chest, and intrathoracic vascular, cardiac, or diaphragmatic injury), abdominal injury (solid viscus, hollow viscus, or vascular injury), extremity injury (greater than 10% body surface area soft tissue injury, vascular injury, nerve injury, or amputation), fracture injury (fracture of extremity, pelvis, face, or skull), admission acute physiology and chronic health evaluation (APACHE II) score, and past medical history of cardiac or pulmonary disease.

Operative procedures. The need for operative procedures on admission, anesthesia time, and location of incision, (cranium, thorax, abdomen, extremity, or fracture) were evaluated.

Ventilatory needs. Need for emergent intubation (at the scene or on admission to the emergency room, or intensive care unit), documented aspiration on intubation, failed attempt at extubation before tracheostomy, duration (days) of mechanical ventilation before and after tracheostomy, frequency of pneumonia (diagnosis requiring five of the following: temperature >101.5° F, white blood cell count $>15,000$ mm^3, inflammatory cells and bacteria on Gram stain, positive sputum culture, and new infiltrate on chest x-ray film), duration of mechanical ventilation after pneumonia was diagnosed, and day pneumonia was diagnosed were considered.

Outcome. Intensive care unit stay (days), hospital stay, complications of tracheostomy (bleeding, infection, pneumothorax, stenosis, and esophageal or innominate

Table IV. Ventilatory factors

Factor	*Group I*	*Group II*
Emergent intubation (%)	72	69
Aspiration (%)	12	7
Failed extubation before tracheostomy (%)	8	14
MVD	12 ± 1*	32 ± 3
MVDBTX	4 ± 0.4*	11 ± 0.4
MVDATX	6 ± 0.7*	22 ± 3
Pneumonia (%)	78†	96
MVDAPDX	6 ± 1*	23 ± 3
DPDX	4 ± 0.3*	6 ± 0.3

MVD, Mechanically ventilated days, *MVDBTX*, mechanically ventilated days before tracheostomy, *MVDATX*, mechanically ventilated days after tracheostomy; *MVDAPDX*, mechanically ventilated days after pneumonia diagnosed, *DPDX*, day pneumonia diagnosed

*$p < 0.05$ between groups by Student's t test

†$p < 0.05$ between groups by χ^2 test

Table V. Outcome factors

Factor	*Group I*	*Group II*
Death of injury (%)	18	23
Death of tracheostomy (%)	0	0
Tracheostomy morbidity (%)	4	4
Intensive care unit days	16 ± 1*	37 ± 4
Hospital days	34 ± 4*	51 ± 4*

*$p < 0.05$ between groups by Student's t test

Table VI. Outcome factors

	Tracheostomy within 2 days (n = 12)	*Tracheostomy between days 3 and 7 (n = 39)*
Incidence of pneumonia (%)	50*	85
MVD	15 ± 5	13 ± 1
ICUD	19 ± 5	15 ± 1
HD	31 ± 6	35 ± 5

MVD, Mechanically ventilated days, *ICUD*, intensive care unit days, *HD*, hospital days
*$p < 0.05$ between groups by Student's t test

fistula as a result of tracheostomy), and mortality rates were evaluated.

Statistics. Statistical analyses for continuous variables were performed with the Student t test and discreet variables were analyzed with the χ^2 test, with a p value <0.05 considered to be statistically significant. Data are presented as mean ± SEM.

RESULTS

In a 12-month period, 264 (19%) of 1350 patients with multiple injuries required mechanical ventilation. Thirty-eight of these patients (14%) died within 24 hours of admission and 120 of 264 (46%) were successfully disengaged from the ventilator (55 patients within 2 days, 50 patients between days 3 to 7, 10 patients between days 8 to 14, and five patients between days 15 to 21). One hundred six patients (40%) were prospectively, consecutively allocated by the date of admission into one of two groups. Group I (51/106; 48%) underwent tracheostomy within 7 days of admission to the intensive care unit. In this group 24% (12/51) underwent tracheostomy within 2 days (1 ± 0.1 day), with 76% (39/51) undergoing the procedure between days 3 through 7 (5 ± 0.4 days). Patients in group II (55/106; 52%) underwent tracheostomy after 8 days of admission to the intensive care unit. Eighty-two percent of these patients underwent tracheostomy between days 8 and 14 (10 ± 0.1 days), and 18% (10/55) underwent tracheostomy between days 15 and 21 (16 ± 0.1 days).

When admission factors were compared between groups (Table I), there were no significant difference in age (36 vs 39 years), gender (41 vs 43 men), injury type (90% vs 95% blunt injuries), Injury Severity Score (28 vs 27), admission Glasgow Coma Score (identical at 10), or hypotension on admission (35% vs 47%).

Distribution of injury sites was similar (Table II). Admission Apache II scores were identical.[10] Past medical history of pulmonary or cardiovascular disease was found in 12% of patients in group I and 15% of patients in group II.

Seventy-six percent of patients in group I required immediate operation compared with 73% of patients in group II (difference not significant). There were no significant differences in duration of anesthesia or the distribution of incision sites (Table III).

There was a statistically significant reduction in duration of mechanical ventilation favoring the early tracheostomy group (Table IV). In addition, fewer days of mechanical ventilation were required after tracheostomy in group I. Both the incidence of pneumonia and the days of ventilation required after pneumonia was diagnosed were reduced in the early tracheostomy group.

Death as a result of injury occurred in 18% of patients in group I and 23% of patients in group II (difference not significant). There were no deaths attributable to tracheostomy in either group. Intubation-related morbidity was equivalent and consisted of one severe infection and one incident of tracheal stenosis in each group.

Statistically significant reductions in duration of stay in the intensive care unit and hospital stay were realized

Table VII. Outcome factors

	Group I $n = 39$	*Group II* $n = 55$
Pneumonia	84%	96%
MVD	12 ± 18*	37 ± 3
Intensive care unit days	14 ± 1*	37 ± 4
Hospital days	35 ± 5*	51 ± 4

*$p < 0.05$ between groups Student's *t* test

with early tracheostomy (Table V). Further analysis of the data demonstrates that the incidence of pneumonia is significantly lower in the small group of patients who underwent tracheostomy within the first 2 days compared with the patients who underwent the procedure between days 3 and 7 (Table VI), but with no significant reduction in the other outcome variables. Yet comparing the 39 patients who underwent tracheostomy between days 3 and 7 to the patients in group II (tracheostomy after day 8), the incidence of pneumonia is similar, but a statistically significant reduction exists in the total number of days spent on a mechanical ventilator, in intensive care, and in the hospital with early tracheostomy (Table VII). This finding supports the value of delaying tracheostomy for 3 to 5 days to attempt extubation and of performing the procedure on or before day 7 of mechanical ventilation to realize its benefit.

DISCUSSION

Despite its long history and widespread use in the critical care setting, tracheostomy continues to be considered a procedure of last resort to be used only when a prolonged trial of translaryngeal intubation fails. In 1986 the American College of Chest Physician's Council on Critical Care[14] recommended "trans-laryngeal intubation for patients requiring assisted ventilation for less than 7 days . . . but if extubation cannot be foreseen on the seventh day, conversion to tracheostomy should be strongly considered." In 1989 a consensus conference[15] opined that the disadvantages of tracheostomy include (1) cost and (2) complications attributed to the procedure. The conference proceedings recommended that "for artificial airway for up to 10 days, the trans-laryngeal route is preferred. For anticipated need of the artificial airway for greater than 21 days, tracheostomy is preferred."[15] These conclusions have been drawn from retrospective analyses of disparate patient groups within multispecialty critical care settings. The data are biased toward long periods of translaryngeal intubation. More important, outcome factor analysis has been based on outdated moribdity and mortality figures.

During the past 30 years, these data have done little to determine if timing of tracheostomy plays a role in managing the critically ill patient. Stock et al.[12] observed: "In our experience a tracheostomy may allow for earlier discharge from the ICU without increased total hospital days." Our study, involving a homogenous patient population admitted to a surgical critical care setting after multiple trauma reveals several important points: (1) tracheostomy can be performed with no deaths as a result of the procedure; (2) the morbidity rate of tracheostomy is low (4%) and equivalent to that of translaryngeal intubation; (3) early tracheostomy in the patient with multiple trauma decreases total days on the ventilator, intensive care unit days, and hospital stay; (4) the diagnosis of pneumonia is confirmed earlier with tracheostomy; (5) the incidence of pneumonia is decreased only if tracheostomy is performed within the first 48 hours but to no advantage in decreasing intensive care or hospital stay; and (6) tracheostomy performed after day 3 but before day 7 did not decrease the incidence of pneumonia but did significantly decrease total days on the ventilator and intensive care and hospital stay. Early tracheostomy benefits the severely injured patient who requires more than 7 days of mechanical ventilation. Not only are morbidity and mortality rates low but also intensive care and hospital stay is decreased, thus reducing hospital cost.

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Surgical Research Society Abstracts

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The 72nd meeting of the Surgical Research Society took place at Southampton University on 5–6 July 1990. The meeting was organized by the University Department of Surgery and 100 papers were delivered. Professor Browse presided and the Patey Prize for the best paper presented in the plenary session by a young researcher was awarded to Mr N. C. Hickey for his paper on 'Prolonged improvement in femorodistal graft flow after single bolus injection of iloprost'.

Management of screen-detected breast cancer – the importance of residual disease

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The National Breast Cancer Screening Programme will detect a new group of breast cancers, behaviour of which is currently uncertain. Proposed national studies on management of these tumours are likely to require complete excision of the reference lesion as a prerequisite for conservation surgery. We have investigated the histopathological characteristics of 100 consecutive patients with screen-detected breast cancer in relation to residual disease.

Tumour type, size, grade, resection margins and extent of primary or associated *in situ* disease were all assessed by one pathologist Thirty-seven women required further surgery (wider excision or mastectomy) and the resected specimen examined for residual *in situ* or invasive cancer.

In total, 21 women had residual cancer (57 per cent) in the resected specimen. Of those with initial disease at the resection margin 16/25 (64 per cent) had residual disease Five (42 per cent) of those with disease close to (within 2–3 mm) but not at the margin had residual disease. Of those with an extensive *in situ* component, 19/26 had residual disease (12/15 of those undergoing mastectomy), whereas only 2/11 women with none or some *in situ* disease had residual cancer ($P<0{\cdot}01$).

In screen-detected breast cancer, residual cancer was present in 73 per cent of women with an extensive *in situ* component at initial surgery. These women comprise a group in which conservation surgery is inappropriate if completeness of excision is considered a prerequisite.

Use of the ultra-thin choledochoscope in cholecystectomy

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Peroperative cholangiography is now a routine part of cholecystectomy. However, equivocal radiological findings result in a negative common bile duct exploration rate of 22–35 per cent. We have evaluated an ultra-thin choledochoscope, inserted via the cystic duct, which may reduce the negative exploration rate.

Eighty patients, 58 females and 22 males with a median age of 57 years, undergoing routine cholecystectomy had peroperative cholangiography and ultra-thin choledochoscopy. The ultra-thin choledochoscope could be passed in 69 (86 per cent) of the patients but useful views were obtained in only 67, the median time for examination being 9 (3–15) min. Five patients with common bile duct stones were identified by both methods, 53 patients being normal by both methods.

In nine patients with equivocal cholangiograms, three had calculi confirmed at choledochoscopy, six were normal and did not proceed to common bile duct exploration. With an average follow-up of 18 months all patients remain well. Overall, 12 per cent underwent common bile duct exploration. There were no negative explorations.

Ultra-thin choledochoscopy is a useful adjunct to cholangiography particularly where the radiological findings are equivocal.

Role of hydroxyl and superoxide free radicals in reperfusion injury

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Free radicals are potential mediators of reperfusion injury following revascularization of an acutely ischaemic limb. Thus, 30 min prior to release of a tourniquet applied to one hind limb of rats for 6 h, 12 animals commenced i.v. dimethylthiourea (DMTU – hydroxyl scavenger) at 500 mg kg^{-1} h^{-1}, 12 rats started superoxide dismutase at 35 000 IU kg^{-1} h^{-1} and catalase at 400 000 IU kg^{-1} h^{-1} (SD+C – superoxide scavenger) whilst 12 control animals received no infusion and 10 normal animals were studied without preceding ischaemia

Following tourniquet release, gastrocnemius muscle blood flow was assessed by i a. injection of radioactive microspheres (^{46}Sc; ^{85}St; ^{141}Ce) 10, 120 and 240 min after tourniquet release. A perfusion index was calculated between the reperfused and contralateral limb.

Treatment	n	Perfusion index at 10 min	120 min	240 min
Normal	10	1·05(0·68–1·18)†	0·97(0·79–1·13)†	1·01(0·73–1·16)†
Control	12	0·12(0·02–0·43)*†	0·48(0·11–0·70)*†	0·05(0·01–0·38)†
DMTU	12	0·10(0·03–0·15)	0·04(0·02–0·21)*	0·04(0·00–0·11)
SD+C	12	0·94(0·54–1·21)*	0·66(0·42–1·01)	0·27(0·01–0·35)
		*$P<0{\cdot}01$ †$P<0{\cdot}01$	*$P<0{\cdot}01$ †$P<0{\cdot}05$	†$P<0.01$

Results are median+i.q. range, Mann–Whitney U test

Control animals, compared to normals, demonstrated low reflow (10 min) relative reperfusion (120 min) and reperfusion injury (240 min). Low reflow was abolished by SD+C, perhaps by preservation of nitrous oxide (endothelial-derived relaxing factor) which is annihilated by superoxide radicals. In contrast DMTU did not improve gastrocnemius muscle blood flow at either 10 or 240 min and abolished relative reperfusion at 120 min, indicating that hydroxyl radicals are involved in pathways increasing skeletal muscle blood flow following ischaemic injury and are thus beneficial.

Absorption and motility after ileal mucosal fenestration and colonic autotransplantation (IMFCA)

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Small bowel allotransplantation has formidable immunological reactions. This study has devised and tested a method of small bowel augmentation by mucosal autotransplantation (IMFCA).

In 10 test pigs, a 12 cm isolated ileal loop with an intact vascular pedicle was denuded of muscle, fenestrated, expanded to 20 cm and autotransplanted into a 20 cm loop of colon which had been stripped of its mucosa (IMFCA). Thus, a composite loop of fenestrated ileal mucosa grafted upon colonic muscle, was constructed by IMFCA, as a Thiry-Vella (TV) fistula. In eight control pigs, TV fistulae of both normal ileum (12 cm) and colon (20 cm) were constructed. After healing, the degree of mucosal expansion, the absorptive capacity and the motility of IMFCA loops were then evaluated against the control.

In IMFCA loops, fenestrations healed by neomucosal ingrowth. The IMFCA mucosal surface area at 14 weeks after surgery measured (mean±s.e.m.) 85·3±9·4 cm^2 compared to 45·9±0·7 cm^2 for the original 12 cm ileal loops. Fatty acid absorption by IMFCA neomucosa was histochemically indistinguishable from that of control ileal mucosa. Motility functions, including the peristaltic reflex, spontaneous contractile activity and response to sennoside stimulation were similar in IMFCA and control bowel loops

IMFCA yields 85 per cent expansion of absorptive ileal mucosa, with support by intact colonic motility It appears a promising means of small bowel augmentation.

Effect of endothelial cell seeding on graft thrombogenicity and early patency

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Endothelial cell seeding has been proposed as a method for improving the long and short term patency of prosthetic vascular grafts. We report on the effect of endothelial cell seeding on the deposition of platelets on ePTFE grafts in dogs. External jugular veins from five dogs were

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used to obtain endothelial cells. Cells were grown to confluence in tissue culture and then seeded onto fibronectin-coated ePTFE grafts of 4 mm diameter. Each dog then received a graft seeded with its own cells and a contralateral, non-seeded, control graft. The grafts were placed as interposition femoral grafts.

One week after implantation, autologous platelets were labelled with ^{111}Indium oxine and the thrombogenicity index (TI) of each graft was determined over a one week period. The mean TI for seeded grafts was 0·123±0·019 (mean±s.d.) and that for the controls 0·183±0·017 (P=0·004). All grafts were patent at 1 week but all control grafts occluded between 6 and 12 weeks. Only one seeded graft had occluded by 12 weeks (P=0·0238). In conclusion, we have shown that endothelial cell seeding significantly reduces the early thrombogenicity of ePTFE grafts which in turn improves their short term patency.

Prospective, randomized controlled trial of endoscopic intubation and laser recanalization in the treatment of malignant dysphagia

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Forty consecutive patients, presenting with malignant dysphagia and who were unsuitable for curative therapy, were randomized to receive either endoscopic intubation or laser recanalization as their primary treatment. There was no significant difference in patient age, sex, their duration of symptoms, presentation dysphagia grade, reason for palliation, tumour length, histology and site, between groups. Results were analysed on an intention to treat basis.

Laser recanalization was carried out using a neodymium/YAG laser, employing a retrograde technique after initial dilatation to 18 mm if possible. Endoscopic intubation was performed using an 'Atkinson' pulsion prosthesis (Keymed Ltd) after initial dilatation. Endoscopies, intubations and laser recanalizations were performed under titrated sedation of midazolam±pethidine.

All laser patients achieved a lumen. There was, however, one failed intubation. Three patients required initial antegrade recanalization. The best dysphagia grade achieved during follow-up was significantly better in the laser-treated group (P<0·01). There was no significant difference in the overall survival (P>0·05) or in the proportion of that survival spent as an inpatient (P>0·05). Laser patients, however, required more admissions. Complication rates were acceptable in both groups. The results indicate that laser recanalization provides better palliation of dysphagia but without a significant improvement in survival compared to pulsion intubation.

Detection and significance of occult lymph node metastases in node-negative breast cancer

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Lymph node status remains the best single prognostic factor in operable breast cancer, yet the significance of occult nodal metastases (OM) is uncertain. This study sought to define the prognostic significance of immunohistochemically detected OM in patients with 'node-negative' breast cancer. Immunoperoxidase staining was performed on archival formalin-fixed paraffin-embedded tissue using a cocktail of murine anti-mucin antibodies (BC2, BC3, 3E1 2). The primary tumours and axillary lymph nodes of 343 patients with invasive ductal or lobular carcinoma were studied. Survivals were assessed using Kaplan Meier curves with log rank analysis. Median follow-up was 79 months. Axillary OM were detected immunohistochemically in 41 patients (12 per cent). Most OM were micrometastatic (<2 mm), though larger or diffuse deposits occurred in 10 patients (24 per cent). Although many smaller deposits were emboli in the subcapsular sinus, the node parenchyma was invaded in 37/41 cases. Those with OM were significantly more likely to relapse (84 per cent versus 68 per cent at 5 years; χ^2=6·1, 1 df, P=0·014) but an increased mortality was not demonstrated. Blind assessment of repeat haematoxylin and eosin sections detected OM in 10/41 patients. When these were excluded from the analysis, no significant difference in outcome was seen for those with antibody-detected OM. Single level lymph node immunohistochemistry *per se* is not a useful prognostic factor. It does, however, enable more accurate definition of nodal involvement, especially in difficult cases.

Effect of low molecular weight heparin on intimal hyperplasia

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Intimal hyperplasia due to smooth muscle cell proliferation is a well recognized cause of vascular graft failure within the first year. Several studies have now demonstrated that the mitogenic activity of platelet-derived growth factor is modified by heparin. In this study, the efficacy of a low molecular weight heparin (LMWH) in controlling intimal hyperplasia *in vivo* has been assessed. Forty New Zealand White rabbits were used in the study. In 10 animals, dose-dependent pharmacokinetic studies showed that the subcutaneous administration of 60 anti-factor Xa units of LMWH produced measurable anticoagulant activity. In 30 New Zealand White rabbits, aortic intimal hyperplasia was induced by endothelial denudation using a balloon catheter. Animals were assigned to a control group or a treatment group where they received LMWH subcutaneously once or twice daily, for one month. Animals were then killed and the aortas harvested for analysis of vessel wall thickness and the degree of intimal hyperplasia using a computerized image analysis system. The results were as follows.

Treatment	Vessel diameter (mm)	Medial area (mm^2)	Luminal reduction (%)
Controls	2·61 (0·31)	0·61 (0·15)	24·7 (7·33)*
LMWH once daily	2·71 (0·14)	0·66 (0·13)	8·44 (4·95)**
LMWH twice daily	2·65 (0·20)	0·59 (0·11)	8·25 (3·40)**

S.d. given in parentheses. * Controls versus treated P<0·001. ** LMWH once daily versus LMWH twice daily not significant

The results of this study demonstrate for the first time that subcutaneous LMWH given once or twice daily was effective in preventing the development of intimal hyperplasia.

Circulating lymphokine levels and amino acid clearances following liver transplantation (LTx)

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Interleukin-2 (IL-2) is essential for normal T and B cell response to antigen, exerting its effects through specific receptors, released in a soluble form following activation (IL-2R). Daily IL-2 and IL-2R levels (measured by ELISA) and central plasma clearance rates of amino acids (CPCR-AA) were determined in liver transplant (LTx) recipients. Results were related to needle biopsy appearances and the clinical course (expressed below as mean±standard error).

Patient group	Plasma IL-2 (ng ml^{-1})	Biliary IL-2 (ng ml^{-1})	Plasma IL-2R (U ml^{-1})	CPCR-AA ml m^{-2} min^{-1}
Normal	0·8±0·3 (n=42)	—	385±42 (n=30)	68±11 (n=15)
Stable LTx	2·8±0·5 (n=25)	3·2±1·1 (n=12)	503±61 (n=20)	263±22 (n=20)
Cytomegalovirus infection	36·4±9·1 (n=15)	29·5±11·5 (n=10)	2164±162 (n=15)	186±37 (n=12)
Moderate injury	51·4±11·8 (n=18)	76·2±25·5 (n=12)	2012±140 (n=18)	195±15 (n=12)
Severe injury	58·6±12·3 (n=15)	41·5±18·3 (n=12)	1985±122 (n=15)	93±18 (n=10)

Infection and cellular injury of the LTx resulted in significant elevation of IL-2 and IL-2R levels compared with stable allografts (P<0·05, Mann–Whitney U test). Amino acid clearance was not, however, significantly reduced except in those livers with severe injury (P<0·05), all of which required retransplantation.

Renal allograft biopsy using real time ultrasound guidance

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Renal transplant biopsy is a commonly performed technique which is not without risk to the transplant or the patient. The ideal biopsy technique provides a core of renal cortex without damaging the allograft. This study compares the success and complication rates of two techniques: a blind vertical pass Tru-cut biopsy method (BVP) and a technique using an automatic biopsy gun and incorporating real time ultrasound scanning to guide the Tru-cut needle (USG).

Two consecutive series of 100 renal transplant biopsies obtained by the BVP and USG biopsy techniques were compared by histological assessment. The results (*Table*) demonstrate that the ultrasound-guided technique was significantly more successful in achieving the aim of sampling the renal cortex.

	Renal cortex in biopsy	
	+	−
USG	88	12
BVP	64	36

$\chi^2=15\cdot789$ (df=1), $P<0\cdot001$

The mean glomerular count per biopsy was 15 in the ultrasound group and 5 in the vertical pass group ($P<0\cdot001$, Mann–Whitney *U* test). Macroscopic haematuria occurred in seven cases in the ultrasound group and in five cases in the vertical pass group.

Ultrasound-guided biopsy yields a higher percentage of adequate biopsies compared to the vertical pass technique. This technique should be adopted for all transplant biopsies.

Lymphocyte immunotoxin active against graft versus host disease in small intestinal transplantation

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The immunocompetent T lymphocytes transplanted with a small bowel allograft have the potential to cause graft versus host disease (GVHD). In this study grafts have been pretreated with a specific anti-T cell monoclonal antibody (OX19) conjugated to ricin A chain to test the efficacy of this immunotoxin in reducing GVHD. Small bowel transplants were carried out in inbred rat strains between parent (PVG) and F1 hybrid offspring (PVGxDA), a model in which GVHD occurs without rejection. After harvesting, grafts were perfused with Marshall's solution (groups 1+2), OX19, a specific T cell monoclonal antibody (group 3), or an immunotoxin comprising OX19 bound to ricin A chain (groups 4+5) After 30 min cold incubation, each graft was flushed with Marshall's solution then transplanted into a heterotopic position in the recipient. Animals in groups 2+5 received cyclosporin A (CsA) after operation (5 mg kg^{-1} day^{-1} for 14 days, then 5 mg kg^{-1} twice weekly)

Group	Treatment	Median survival (days)	Wilcoxon rank sum test
1	Control	20	—
2	CsA	32	$P<0\cdot05$
3	OX19 control	21	n.s.
4	Immunotoxin	37	$P<0\cdot05$
5	Immunotoxin+CsA	50	$P<0\cdot01$

Fully allogeneic transplants were then carried out between two inbred rat strains (PVG→DA). Animals were killed at 7 days. A monoclonal antibody binding exclusively to PVG rat cells (OX27) was used with immunohistochemistry to identify graft cells in the spleen.

Treatment	Graft cells in host spleen (%)	
CsA	47	$P<0\cdot01$ (Wilcoxon)
CsA+immunotoxin	39	

Migration to the host can be reduced by graft perfusion with a toxin-conjugated monoclonal antibody. This procedure is feasible in clinical small bowel transplantation and would be a realistic strategy for preventing GVHD.

Effect of small bowel transplantation on small intestinal microflora in the rat

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We have investigated the quantitative and qualitative changes in the microflora of the rat small intestine following heterotopic transplantation of a small bowel isograft. Following vascular anastomoses the bowel ends were exteriorized. The graft vasculature was perfused with Marshall's solution at 4°C and the lumen flushed with 20 ml 0·05 per cent chlorhexidine solution. All animals were given 1 mg gentamicin subcutaneously postoperatively Groups of animals ($n=6$) were killed at 2, 7 and 28 days. The native bowel (host) and the graft intestine (graft) were removed and flushed with 10 ml sterile saline. The effluents were mixed and serially diluted 10:1. Aliquots of 1 ml of each of five serial dilutions were subjected to aerobic and anaerobic culture at 37°C. Resulting colonies were counted and subcultured on nutrient strips for identification.

	$10^{-6}\times$ Bacterial counts (cells) at					
Intestine	2 days		7 days		28 days	
Host	6·3	$P<0\cdot05$	9·0	$P<0\cdot01$	6·6	n.s.
Graft	170·0		350·0		9·6	

Wilcoxon rank sum test on $\log_{10}$ per g dry weight of bowel

At 2 days and 7 days the predominant organisms in both the host and graft were aerobic faecal organisms and normal skin commensals. However, by 28 days these organisms were replaced in both the native bowel and the transplant loop by *Flavobacterium meningosepticum*, a potentially pathogenic organism. The combined effects of cold storage and ischaemic injury on small bowel transplants in the rat lead to increased numbers of bacteria in the graft in the early stages post-transplant followed by an overgrowth of non-enteric organisms in both the graft and host after 28 days.

Helicobacter pylori in renal transplant recipients

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It has been recognized for over 20 years that peptic ulceration and related pathologies occur with increased frequency in renal transplant recipients. The aetiology is unclear, but is thought to be related to increased gastric acid secretion and corticosteroid administration.

We have studied *Helicobacter pylori* in 33 unselected transplant recipients who underwent upper gastrointestinal endoscopy at between 2 and 4 months after transplantation. Random gastric and duodenal biopsies were obtained and were subjected to histological examination and urease slide test analysis.

The mean age of the patients was 41 and the prevalence of *H pylori* and the relationship to symptomatic dyspepsia is summarized in the *Table*

	Prevalence of *Helicobacter pylori*		
	Symptomatic ($n=20$)	Asymptomatic ($n=13$)	Total ($n=33$)
Urease slide test (gastric)	10	1	11
Histology (gastric)	12	3	15
Histology (duodenal)	2	0	2
Total patients colonized	13	3*	16

*$P<0\cdot05$

H. pylori was significantly associated with antral gastritis, but not with other gastrointestinal pathologies There was no relationship between *H pylori* and age, renal function, serum cyclosporine levels or prednisolone dose.

In conclusion, we have demonstrated *H pylori* in 48 per cent of renal transplant recipients and have demonstrated a significant association with symptomatic dyspepsia ($P<0{\cdot}05$) It is possible, therefore, that the immunosuppressive regime may predispose these patients to a high risk of *H. pylori* infection.

Effect of interferon-gamma on upregulation of T lymphocytes in health and malignancy

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Interferon gamma (IFN-γ) is a pivotal cytokine of immunoregulation. Phase I/II trials administering IFN-γ to patients with advanced solid malignancies have been disappointing The aim of this study was to determine if IFN-γ upregulates resting and activated T lymphocytes in health and malignancy.

Nineteen patients with colorectal cancer were venesected pre-operatively at the same time as 19 healthy volunteers. Separated lymphocytes were cultured with or without the mitogen concanavalin A (ConA) and 200 U ml^{-1} recombinant human IFN-γ (rHuIFN-γ) were added to half the lymphocytes in each assay Two assays were performed: one to determine expression of interleukin-2 receptors (IL2R) and class II MHC molecules (HLA-DR) using flow cytometry; and the other to measure lymphoproliferation Results are expressed as median [range] and the Wilcoxon paired rank sum test was used. rHuIFN-γ resulted in a significant increase in HLA-DR expression on resting T cells in the control (−rHuIFN-γ = 11 per cent [3–24] versus +rHuIFN-γ = 12 [5–29] $P<0{\cdot}02$) and tumour group (−rHuIFN-γ = 11 [7–28] versus +rHuIFN-γ = 17 [6–35] $P<0{\cdot}02$). Following activation of T cells by ConA this increase of HLA-DR expression was seen in the control (−rHuIFN-γ = 23 [6–50] versus +rHuIFN-γ = 30 [11–67] $P<0{\cdot}05$) but not the tumour group. rHuIFN-γ had no significant effect upon IL2R expression or lymphocyte proliferation in any group. rHuIFN-γ alone is unable to activate T lymphocytes The upregulation of HLA-DR demonstrates a further immunoregulatory role for IFN-γ, which is impaired in malignancy. The synergistic effect of IFN-γ with IL-2 and other cytokines needs to be explored

Effect of diet deficient in linoleic acid on gastric and duodenal eicosanoid synthesis in the rat

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Patients with duodenal ulcer have a reduced ability to synthesize gastric and duodenal mucosal prostaglandins compared to non-ulcer control patients This study investigates the effect of a diet low in essential fatty acids on mucosal eicosanoid synthesis. Male Wistar rats were raised on a standard diet containing 51 per cent of the fat content as polyunsaturates Half the rats were then fed a deficient diet in which only 9 per cent of the fat content was polyunsaturates The other half were maintained on the standard diet. Eight rats in each group were killed at the start of the study and at two-weekly intervals thereafter for six weeks Measurement of eicosanoids in the mucosal incubates was by radioimmunoassay. After six weeks on the deficient diet gastric prostaglandin E_2 production fell from a mean of 9·24 ± 2·5 ng mg^{-1} protein to 1·14 ± 0·42 ng mg^{-1} protein, gastric thromboxane A_2 from 3·71 ± 0·83 ng mg^{-1} protein to 0·37 ± 0·13 ng mg^{-1} protein and gastric prostacyclin from 29·03 ± 9·60 to 3·02 ± 0·83 ng mg^{-1} protein. Similar changes occurred in the duodenal mucosa No decrease in eicosanoid synthesis was observed in rats maintained on the control diet. Consumption of a diet with a high saturated fat content and a low polyunsaturated fat content may explain the reduced capacity of duodenal ulcer patients to synthesize mucosal eicosanoids

Sutures or staples in gastrointestinal surgery – a prospective randomized comparison

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This prospective, randomized clinical trial compared manual suturing and surgical stapling techniques in gastrointestinal surgery.

Over 4 years, 1161 consecutive patients were studied, of whom 1004 had their anastomoses randomized, 496 to suturing and 508 to stapling. Antibiotic prophylaxis, bowel preparation, anastomotic materials and technique were standardized by prior agreement. Assessment of anastomotic integrity included contrast radiography for oesophageal and colorectal anastomoses.

There was no significant difference in the incidence of clinically evident leaks between the sutured and stapled groups (3·2 per cent versus 4·1 per cent respectively, $P=0{\cdot}22$) Patients with sutured oesophageal and colorectal anastomoses had a significantly higher incidence of radiological leaks than their stapled counterparts (12·2 per cent versus 4·1 per cent, $P<0{\cdot}02$). Surgical stapling resulted in significantly quicker anastomoses (28·1 ± 0·7 versus 14·3 ± 0·5 min, $p<0{\cdot}001$) and operations (155·5 ± 2·4 versus 103·9 ± 2·2 min, $P<0{\cdot}001$). No other significant differences were noted between the two groups

These findings demonstrate that surgical stapling results in significant time saving and lower incidence of subclinical, radiological leaks compared with manual suturing techniques. In all other respects both anastomotic techniques were comparable

Artificial oesophagus and a new device for measuring lower oesophageal sphincter function

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Lower oesophageal sphincter (LOS) competence depends upon both length and pressure. Existing devices can measure length and pressure, but not simultaneously This methodological problem is a fundamental drawback to understanding LOS function and its role in oesophageal disease.

A 'sphinctometer' has been developed consisting of an oil-filled 2·5 mm diameter silastic chamber, 6 cm in length incorporating a solid-state pressure transducer designed to provide an integrated pressure reading as a function of length. Its performance has been tested *in vitro* using human cadaver oesophagus in a specially constructed chamber in which sphincter length and pressure can be independently varied. Comparisons were made with a conventional pull-through technique.

	Sphincter length (cm) at pull-through pressure (mmHg) of				
	10	20	30	40	50
1	2	4·5	7·5	10·5	13·5
2	4	8·3	12·5	17·5	24·5
3	6	12	18·5	24	31
4	8	16·5	25	33·5	42
5	11	21	31	41	51

Sphinctometer response was linear throughout the range 0–50 mmHg ($r=0{\cdot}99$). The device is thus suitable for determining the function of the human LOS and has subsequently been incorporated into an ambulatory system for patient use Such a device has the potential to correctly elucidate the role of the LOS in oesophageal disease.

Nissen fundoplication – the potential for improvement

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Recurrent reflux and dysphagia are the major causes of failure of Nissen fundoplication These usually result from wrap disruption or migration. In an attempt to promote wrap stability, we assessed the effect of using porcine dermis (Zenoderm) to reinforce the repair

Thirty-eight patients were randomly allocated to receive either a standard floppy Nissen fundoplication (20), or a short (1 cm) fundoplication supported by a 3 × 1 cm strip of Zenoderm (18) Median follow-up was 12 months (range 2–23).

There was no perioperative mortality or significant morbidity. Thirty-four (89 per cent) of patients had a satisfactory symptomatic result (Visick 1/2) Three patients in the standard group had objective evidence (endoscopy/prolonged pH studies) or recurrent reflux, in contrast to one patient in the Zenoderm group ($P=0{\cdot}27$; Fisher's exact test) Early postfundoplication dysphagia was less common in the Zenoderm group (4/18) than in those who underwent standard fundoplication (11/20) ($P=0{\cdot}083$; χ^2 test).

These preliminary results suggest that the outcome of Nissen fundoplication can be improved by simple technical modification. Further recruitment to this trial is required to validate these results.

Resection line disease in gastric cancer – a continuing problem

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Surgery is the only effective treatment for gastric cancer and complete excision is the aim Involvement of the resection margins is known to increase anastomotic dehiscence and perioperative survival[1] and impair long-term survival[2]. The operative findings from 563 patients referred to the second British Stomach Cancer Group trial has been used to determine the operative stage and this has been compared with the incidence of resection line disease.

There were 67 patients who were considered to have stage I disease, 110 stage II, 251 stage III and 135 stage IVa. Resection line disease was identified in the distal margin in 27 cases, in the proximal margin in 60 cases and in both margins in 18. Involvement of a resection margin was found in 10 per cent of the cases considered to be stage I, 12 per cent of stage II cases, 14 per cent of stage III cases and 37 per cent of the stage IVa cases. Overall, 13 per cent of curative resections became palliative procedures.

Despite awareness of the risks associated with resection margin involvement, surgeons are performing inadequate surgery in patients considered to have curable disease. A more aggressive approach to intraoperative assessment is necessary to reduce the incidence of resection margin involvement.

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Serum suppression of LAK cell generation in patients with metastatic gastrointestinal cancer

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Response rates of the order of 20 per cent are obtained using high-dose interleukin-2 (IL-2) alone to treat patients with metastatic malignant melanoma (MM) or renal cell cancer (RC). The addition of adoptive immunotherapy with autologous *ex vivo* lymphokine-activated killer (LAK) cells does not improve these response rates. Conversely, using IL-2 alone, no clinical responses are observed in patients with gastrointestinal cancer (GIC), but 17 per cent of such patients will respond if autologous LAK therapy is added to high-dose IL-2. We have inquired whether these observations are explicable by the suppression of IL-2-induced LAK cell generation by serum factors in patients with metastatic GIC

Serum from 85 patients (30 with metastatic GIC, 23 with localized GIC, 14 with metastatic MM or RC, and 18 age-matched healthy controls) was added to Il-2-stimulated LAK cultures using peripheral lymphocytes from healthy individuals. LAK cytotoxicity was measured 3 days later using ^{51}Cr-labelled DAUDI cells as targets.

Serum suppressive activity was defined as cytolysis which was below the 95 per cent confidence limits for control sera (i.e. $P<0\cdot05$). By this criterion, 1/18 (6 per cent) control serum, 2/14 (18 per cent) MM or RC sera, 4/23 (17 per cent) localized GIC sera and 17/30 (57 per cent) metastatic GIC sera were suppressive.

Serum-mediated suppression of LAK generation may be a factor in the failure of advanced GIC to respond to IL-2 suggesting that IL-2 therapy should be administered earlier in the disease.

Immunotherapy via isolated organ perfusion

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Interleukin 2 (IL-2) combined with lymphokine activated killer cells (LAK) can produce significant tumour regression. Unfortunately the high concentrations of IL-2 required for optimal therapeutic effect has resulted in severe toxicity due to increased vascular permeability. In using an isolated organ perfusion technique the therapy can be targeted to the tumour cells while avoiding systemic toxicity.

In this study, irradiated, 5-week-old nude rats were injected intrabronchially with 10^7 human H460 large cell carcinoma cells. After 3 weeks, lungs containing tumours were removed and underwent isolated perfusion for 1 h, under sterile conditions, with either Krebs Henseleit salt solution (control), 5×10^7 LAK cells with 500 U ml^{-1} IL-2, or 100 μg ml^{-1} adriamycin as a control tumourocidal therapy. After perfusion, tumours were disaggregated with collagenase/DNAase and plated out in soft agar for a clonogenic assay of cell kill.

The disaggregated tumours were similar in all groups. tumour weights 0·35–0·50 g; cell yield $3\cdot5$–$5\cdot0\times10^7$ cells g^{-1}; tumour cells 20–30 per cent. Average plating efficiencies after 21 days were: control $0\cdot99\pm0\cdot18$ ($n=20$); adriamycin-treated $0\cdot02\pm0\cdot09$ ($n=17$, $P<0\cdot001$ versus control) and LAK/IL-2-treated $0\cdot58\pm0\cdot25$ ($n=18$, $P<0\cdot05$ versus control).

These results show that a 1 h perfusion with immunotherapy or high concentration chemotherapy significantly reduced tumour cell clonogenicity, indicating significant tumour cell kill. In conclusion, isolated perfusion has been shown, in this model, to be a viable option to target LAK cells and IL-2 to tumour cells, and to produce significant tumour cell kill.

Blood transfusion immunomodulation – macrophage prostaglandin E_2 production

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Blood transfusion can cause immunosupression which may increase postoperative problems such as infection and cancer recurrence. The macrophage regulates the immune system and this study examines effects of various blood transfusions on prostaglandin E_2 (PGE2) production by rat macrophages. Inbred Lewis rats were divided into eight experimental groups. On day 0, seven were transfused under general anaesthesia. Donor blood anticoagulated with citrate–phosphate-dextrose was transfused immediately or after storage for 24 h at 4°C. Serum was obtained from the same inbred rats or allogeneic DA rats. On day 4, brain–heart infusate was injected intraperitoneally. On day 7, the elicited peritoneal cells were harvested and cultured for 1 h; non-adherent cells were removed and fresh media added. After 20 h, supernatants were frozen and PGE2 measured by radioimmunoassay (*Table*). Macrophages were identified by a non-specific esterase stain; counts were similar in all groups. In allogeneic and syngeneic blood, storage before transfusion was associated with an increased production of PGE2 by elicited macrophages. Storage conditions and genetics of donor blood may both be factors in transfusion-mediated immunosuppression.

	n	PGE2 production (pg/10^6 macrophages)
Untreated control	13	3569(2606)
Anticoagulant alone	12	3863(1997)
Allogeneic fresh blood	12	4637(2803)
Syngeneic fresh blood	11	4528(3261)
Allogeneic stored blood	10	5874(3686)*
Syngeneic stored blood	11	6852(3526)*
Allogeneic serum	12	7956(6580)*
Syngeneic serum	12	5000(3557)

S.d. given in parentheses. * Compared with untreated controls, $P<0\cdot01$: Wilcoxon's rank sum test

Anti-metastatic gene, *nm*23, in human breast cancer: its relationship to nodal status and survival

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The accurate prediction of the outcome for node negative breast cancer patients is the goal of many clinicians dealing with this disease. Much work has focused on oncogenes and growth factors, however a recently described gene, *nm*23, may be a predictor of tumour metastasis. This gene was originally cloned[1] from murine melanoma cell line K1735 and its expression was found to be inversely related to the metastatic potential of the clones. Initial study has demonstrated that its expression in a small number of primary breast cancers correlated with lymph node involvement[2]

We have assessed the level of *nm*23 mRNA expression in a series of 69 human primary breast cancers and related it to lymph-node status, relapse-free survival (RFS) and overall survival Hybridization was carried out using Northern blotting, with hybridization to the human cell line HeLa RNA as internal control *nm*23 mRNA levels correlated significantly with lymph node involvement, 73 per cent of tumours from lymph-node-positive patients demonstrating low levels of expression, whereas only 33 per cent of tumours from lymph-node-negative patients had similarly low levels ($\chi^2=9\cdot5$, $P<0\cdot05$). RFS and overall survival, assessed by the logrank test, demonstrated a significant difference between patients with tumours expression high ($n=37$) and low ($n=32$) levels of *nm*23. Of patients whose tumours have high *nm*23 value, 71 per cent remain free of disease and 79 per cent survive compared with 32 per cent and 45 per cent for those with a low level of expression, ($P=0\cdot0001$ and $P=0\cdot0005$ respectively)

*nm*23 may be a useful prognostic indicator in breast cancers, especially in node-negative patients

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C-myc protein product as a marker of DNA synthesis but not of malignancy in colorectal tissues and tumours

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C-myc is a putative oncogene. *C-myc* gene transcript levels by Northern blotting are reported to be increased in colorectal adenomas and cancers The gene product is a nuclear bound 62 000-M_r phosphoprotein (p62*c-myc*) Measurement of the gene product may be a better indicator of gene function *in vivo* than is measurement of DNA or RNA transcripts.

The mean p62*c-myc* content was measured in units of fluorescence in the G1 and G2 diploid (D) and aneuploid peaks of the cell cycle by multiparameter flow cytometry using the 6E10 monoclonal antibody. Studies were performed on 113 tumour blocks from 87 patients with colorectal cancer, on blocks from four villous adenomas, 52 colorectal mucosa specimens and 7 mucosal specimens from two patients with polyposis coli.

G2D levels of p62*c-myc* were higher in normal mucosa (303 ± 17 units) than in tumours (186 ± 13 units). No differences in peak *c-myc* expression were found in relation to histological grade, ploidy, anatomical site or to *in vivo* bromodeoxyuridine labelling indices. The highest mean levels of p62*c-myc* were found in polyposis coli mucosa (502 ± 63 units, $n=7$).

p62*c-myc* levels are cell cycle related but the protein has not been shown to be a marker of tissue proliferation or of colorectal malignancy. The normal protein may be structurally associated with DNA, but underproduced in tumour cells. Flow cytometry is a valuable tool for studying gene expression through measurement of the protein product.

Effect of SMS 201-995 on serum tumour marker, mitotic index and gastrin immunoreactivity in colorectal cancer

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The long-acting somatostatin analogue, SMS 201-995, has been shown to inhibit some gastrointestinal cancer cells both *in vitro* and *in vivo* The aim of this study was to evaluate the effect of subcutaneously administered SMS 201-995 on the kinetic index of rectal cancer cells Response to this therapy has been assessed using serial serum marker concentration, serial Ki67 and serial gastrin immunoreactivity of the primary tumour.

Twelve patients with rectal carcinoma were each treated for 2 weeks with SMS 201-995, subcutaneously by continuous infusion at a dose of 600 μg/24 h Each patient acted as his own control and a further six untreated patients were studied.

Four patients had elevated pretreatment carcinoembryonic antigen (CEA) levels In two of these four patients, serum CEA levels fell during SMS 201-995 therapy.

In 4/12 patients a significant decrease ($P<0\cdot01$, $P<0\cdot05$, $P<0\cdot05$, $P<0\cdot02$) in Ki67 immunoreactivity was seen during therapy while in the remaining 8 patients there was no significant change in the Ki67 expression. In two patients who had a reduction in Ki67 expression on SMS 201-995 therapy there was also a significant decrease ($P<0\cdot002$, $P<0\cdot001$) in gastrin immunoreactivity of the primary tumour In six control patients an insignificant rise in Ki67 was noted.

We conclude that SMS 201-995 reduces Ki67 (mitotic index) *in vivo* in some patients with rectal carcinoma This is an original and potentially clinically important finding.

Potential doubling time of colorectal cancer

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The potential doubling time (T_{pot}) of a tissue or tumour is the time that it would take for the cell numbers to double if there were no cell loss. The volume doubling time (V_d) exceeds the T_{pot}. The use of flow cytometry and *in vivo* bromodeoxyuridine (BrdU) labelling is a method by which the tumour cell cycle time, the T_{pot} and other kinetic indices may be measured We have previously shown that the T_{pot} of colorectal tumours is often less than ten days, whereas the V_d often exceeds 100 days.

Nu Nu mice were injected in the flank with 2×10^6 viable MC28 rat tumour cells grown in culture Tumours were measured in three dimensions on days 9, 13 and 16 The mean tumour diameter was used to calculate the V_d. Tumours were excised on day 16 4·4 h after *in vivo* labelling with 200 μg of BrdU intraperitoneally. The mean T_{pot} of the tumours on day 16 was 1·7 days The V_d was 3·0 days The tumours were in the exponential phase of cell growth.

In a further experiment, the cell cycle time (T_c) of the MC28 tumour was calculated. Tumours were serially excised between 2 and 29 h after BrdU labelling, and the mid S phase labelling ratio was calculated. The T_c was 26 h

Measurement of the T_{pot} by flow cytometry and BrdU labelling is a valid technique When applied to primary human colorectal tumours *in vivo*, it is apparent that the cell loss factor may often exceed 90 per cent during normal tumour growth.

Near infrared spectroscopy – a new technique for metabolic assessment in peripheral vascular disease

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Existing methods of assessing the peripheral circulation in arterial disease reflect flow in large vessels rather than the state of the end-tissues. We have investigated a new technique, near infrared spectroscopy, to determine whether it can yield metabolic information that may be of use in assesssing patients with peripheral vascular disease This technique can detect changes in concentration of oxy- and deoxyhaemoglobin.

Thirty four patients have been studied eleven patients with severe claudication or critical ischaemia (ankle/brachial index $<0\cdot75$) and twenty three with minimal or no arterial symptoms. Near-infrared light from six laser diodes was transmitted to the calf by a flexible fibreoptic system; emerging light was carried to a photomultiplier tube and photon counter along a second fibreoptic cable A microcomputer data-logging system collected data and calculated the oxygen saturation of haemoglobin (Hb) in the calf muscles. A cuff was then applied above the knee to produce ischaemia; the rate of Hb desaturation was used to calculate the oxygen consumption of the leg After ischaemia, the rate of reoxygenation of calf muscle Hb and time taken to attain 95 per cent peak oxyhaemoglobin level were measured.

	Normal/mild	Severe	P
Oxygen consumption (ml 100 g^{-1} min^{-1})	0·19(0·16–0·23)	0·13(0·05–0·21)	0·05
Postischaemic rate of Hb reoxygenation (μmol l^{-1} min^{-1})	225 (107–357)	74 (31–107)	0·003
Time to 95 per cent peak oxyhaemoglobin level (s)	24 (14–32)	41 (31–80)	0·002

Results are median + interquartile range, Mann–Whitney *U* test

Clear metabolic differences in the calf muscles between claudicants and normal subjects have been demonstrated. Near-infrared spectroscopy offers the possibility of assessing metabolic activity in the tissues of patients with peripheral vascular disease, avoiding the complexities of nuclear magnetic resonance techniques.

Acute reservoir ileitis (pouchitis): are the mucosal morphological changes due to bacterial overgrowth?

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Ileal pouch mucosa in pouchitis exhibits severe villous atrophy and increased epithelial cell proliferation. These changes may represent adaptation to increased pouch luminal bacterial content

To investigate this hypothesis, we have assessed pouchitis by a functional and sigmoidoscopic score and then measured the villous atrophy index (VAI), crypt cell production rate (CCPR) and faecal bacteriology in 24 patients (pouchitis $n=12$, no pouchitis $n=12$) before and after one month's treatment with metronidazole.

Before metronidazole therapy, severe villous atrophy (low VAI) was associated with an increased CCPR ($\rho=-0{\cdot}8$, $P<0{\cdot}001$)**, macroscopic pouchitis ($\rho=-0{\cdot}6$, $P<0{\cdot}001$)** and poor pouch function ($\rho=-0{\cdot}59$, $P<0{\cdot}001$)**. However, VAI was not associated with changes in total anaerobic or aerobic bacterial counts. Following metronidazole therapy for pouchitis, there was a significant decrease in macroscopic pouchitis median (95 per cent confidence interval): pre 4 (3–6) versus post 2 (1–3), $P<0{\cdot}05$* associated with functional improvement ($\rho=0{\cdot}72$, $P<0{\cdot}001$)** villous regrowth: pre 6·55 (5·2–7·2) versus post 11·6 (10·72–12·77), $P<0{\cdot}05$)* and decreased CCPR (cell $crypt^{-1}$ h^{-1}). pre 3·0 (2·2–5·05) versus post 0·8 (0·55–1·15), $P<0{\cdot}05$* These changes were not seen following metronidazole therapy in patients without pouchitis. There was no difference in total anaerobic or aerobic bacterial counts between patients with and without pouchitis, whilst counts of *Escherichia coli*, enterococci and bacteroides did not change after metronidazole therapy.

These data suggest that impaired pouch function in pouchitis may be related to severe villous atrophy, the aetiology of which is not bacterial overgrowth.

*Wilcoxon paired test, **Spearman rank correlation

Thrombosis prophylaxis in total knee replacement: does a simple mechanical method help?

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Of patients undergoing total knee replacement, ≈60 per cent develop postoperative deep vein thrombosis (DVT), the majority being extensive thrombi likely to produce major pulmonary emboli Currently available mechanical devices are not practical in this particularly high risk group because of the nature of the surgery. In this study the efficacy of a recently developed mechanical device, the arterial–venous impulse foot pump, which reduces stasis in the calf and popliteal veins, has been assessed with regards to the prevention of major thrombosis

Fifty nine patients undergoing 60 total knee replacements were randomly allocated to a control group or to a foot pump group. The pump was applied for ten postoperative days after which all patients underwent ipsilateral ascending venography to assess the incidence of DVT.

	No pump ($n=32$)	Pump ($n=28$)
DVT	22 (68·7%)	14 (50%)
Major calf vein DVT	13 (40·6%)	5 (17·8%)
Proximal vein DVT	6 (18·7%)	0

The results shown in the *Table* indicate that this simple device was effective in reducing the frequency of major thrombosis from 19 (59·4 per cent) in the control group to 5 (17·8 per cent) in the pump group, $\chi^2=8{\cdot}508$, $P=0{\cdot}014$. Furthermore it is possible to use this device throughout the postoperative period.

Prediction of response to tamoxifen in elderly patients with breast cancer by ERICA

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A proportion of elderly women with breast cancer respond to tamoxifen and hence avoid the need for surgery We have performed a prospective study to determine whether estimation of ER status by means of fine needle aspiration (FNA) and the oestrogen receptor immunocytochemical assay (ERICA) can accurately predict which patients are most likely to benefit.

FNA of a breast lump was performed in 54 consecutive patients over the age of 70 and confirmed malignancy An ERICA stain was carried out on each aspirate (satisfactory in 46). All patients were started on tamoxifen (20 mg daily) and followed up at two monthly intervals for a median period of 15 months (range 7–25 months).

Twenty nine patients were positive by ERICA and 27 achieved a response (93·1 per cent). Only two progressed (one died after one month and the other responded for 18 months before progressing). Twelve patients were negative by ERICA and only one responded to tamoxifen (for 20 months) whilst 11 progressed (91 per cent). Five patients had mixed ERICA patterns, three responded, one remained static and one patient progressed. (Response rate: ERICA-positive versus ERICA-negative, $P=<0{\cdot}01$).

In this study the presence of an ERICA-positive tumour in women >70 years accurately predicted the response to tamoxifen. We recommend that ERICA staining should be performed on all breast cancers in elderly women. Patients who are ERICA-positive should be treated with tamoxifen whereas ERICA-negative patients should be offered surgery.

Pulmonary thromboxane synthesis is necessary for lung injury following lower limb ischaemia

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Pulmonary damage following reperfusion of ischaemic tissue is mediated by thromboxane (Tx) and characterized by neutrophil sequestration and increased microvascular permeability. The contribution of pulmonary tissue Tx production to reperfusion lung injury was investigated in 75 anaesthetized rats subjected to 4 h of bilateral hindlimb tourniquet ischaemia and 3 h of reperfusion. Plasma TxB_2 (pg ml^{-1}), pulmonary neutrophil infiltration (per 20 high-power fields) and lung water (wet to dry weight ratio) were determined. Thirty minutes before and 90 min after reperfusion, 0·1 ml of saline, a thromboxane synthetase inhibitor (OKY046) or a thromboxane receptor antagonist (SQ29,548) were introduced into the anterior segment of the left lung by fine bore cannula. Sham animals did not undergo ischaemia.

	Sham ($n=16$)	Saline ($n=18$)	OKY046 ($n=19$)	SQ29,548 ($n=21$)
Plasma TxB_2	380±68	2860±748*	3125±865*	2925±790*
Lung neutrophils	49±8	124±19*	59±17	45±12
Wet:dry	4·0±0·1	4·9±0.2*	4·2±0·1	4·2±0·1

*$P<0{\cdot}01$ relative to sham (ANOVA)

The local appliation of OKY046 or SQ29,548 prevented lung injury without affecting ischaemia-induced thromboxane production. Sham animal bronchial administration of OKY046 or SQ29,548 did not affect pulmonary histology or lung water. Following remote tissue ischaemia, the secondary induction of Tx production by the lung was necessary for neutrophil entrapment and subsequent increased microvascular permeability.

Non-steroidal anti-inflammatory drugs and complicated diverticular disease: a case-control study

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Fifty patients (25 male, 25 female) admitted with severe complications of diverticular disease between 1984 and 1988 were compared with two groups of fifty age- and sex-matched controls admitted during the same period. The first control group (A) was randomly selected from all hospital admissions, and the second group (B) from patients with uncomplicated diverticular disease. In the study group, complications comprised pericolic abscess, generalized peritonitis, bleeding and fistula formation. The mean age for all groups was 68 years.

Of the 50 study patients, 24 (48 per cent) were taking non-steroidal anti-inflammatory drugs (NSAIDs) at the time of admission compared with 9 (18 per cent) in control group A and 10 (20 per cent) in control group B Using control group A, the estimated odds ratio for patients with complicated diverticular disease of being on NSAIDs was 4·0 with a 95 per cent confidence interval of 1·46–13·64 ($P<0{\cdot}01$ by McNemar's test for paired binary data). Similarly, when control group B was used, the odds ratio was 3·80 with a 95 per cent confidence interval of 1·37–13·03 ($P<0{\cdot}01$).

These data suggest that there is a strong association between the ingestion of NSAIDs and the development of severe complications of diverticular disease.

Experimental cystic duct occlusion and mucosal ablation as an alternative to cholecystectomy

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Recurrent cholelithiasis is likely after percutaneous cholecystolithotomy, because of cystic duct patency and intact gallbladder function. This study evaluated bipolar electrocoagulation of cystic duct and tetracycline mucosal ablation in canine gallbladders.

Twenty-nine mongrel dogs (15–23 kg) were anaesthetized, and cholecystotomy performed. Sham cannulation or bipolar radiofrequency electrocoagulation (300 mA × 3 s) of cystic duct was performed. Gallbladders were closed over 12Ch Foley catheters, and 20 ml of saline or tetracycline (50 mg ml^{-1}) was instilled. Animals were randomized. group A ($n=5$), sham cannulation and saline; group B ($n=5$), electrocoagulation and saline, group C ($n=5$), sham cannulation and tetracycline; group D ($n=5$), electrocoagulation and tetracycline; group E ($n=5$), electrocoagulation and saline irrigation at day 14, group F ($n=4$), electrocoagulation and tetracycline at day 14 Tube cholecystography was performed at 14 days to assess duct patency Histological examination of gallbladder and biliary tree was performed at 6 weeks.

Cystic duct occlusion occurred in 3/5 of group B, 4/5 of group D, 4/5 in group E and 3/4 in group F Gallbladder mucosal damage occurred in 2/5 of group D and 3/5 in group F. Full gallbladder mucosal ablation was only observed in group F. The biliary tree was otherwise undamaged.

Bipolar electrocoagulation effectively achieved cystic duct obstruction. Used in combination, duct coagulation and delayed tetracycline instillation are safe, and may prevent gallstone recurrence after cholecystolithotomy

Prolonged improvement in femorodistal graft flow after single bolus injection of iloprost

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Blood flow, thrombogenicity and peripheral resistance are determinants of patency in infra-inguinal grafts Iloprost, a stable prostacyclin analogue, is a potent vasodilator with platelet and neutrophil anti-aggregatory properties. It improves patency after topical application to small arterial anastomoses and may therefore be of benefit after vascular reconstruction.

In a pilot study, improvements in flow after femorodistal bypass were dose-related and 300 ng was found to be optimal. Ten patients received 3000 ng of iloprost and flow increased from a mean value of 118 ml min^{-1} to 225·5 ml min^{-1} after 20 min.

Thirty one patients undergoing femorocrural *in situ* saphenous vein bypass for critical ischaemia entered a controlled trial. Graft blood flow was determined by electromagnetic flowmetry prior to skin closure. Iloprost or placebo (in 15 ml saline) was infused into the graft over 2 min, via a proximal vein branch and flow recorded for 20 min. Postoperatively, graft blood flow was measured by daily Duplex ultrasound examination for 7 days Iloprost produced an immediate improvement in flow, with a mean increase of 94 per cent at 20 min, compared to 6 per cent in controls ($P<0{\cdot}0001$, Student's t test). This significant improvement in flow was maintained over 7 days ($F=5{\cdot}2$, $P=0{\cdot}03$, analysis of variance).

Iloprost appears to attenuate the 'low-reflow' phenomenon after femorodistal reconstruction for critical ischaemia and should therefore reduce the incidence of early graft failure

Cell cycle kinetics and prognosis in early breast cancer

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Thymidine labelling index (TLI) identifies cells in S phase of the cell cycle whereas *in vivo* bromodeoxyuridine (BrdU) labelling also measures movement of cells through the cycle. We report the prognostic value of TLI and describe its relationship to BrdU labelling.

Between 1978 and 1981, TLI was measured in 190 breast cancers by pulse labelling Since 1989, tumours labelled *in vivo* with BrdU were processed by flow cytometry. BrdU labelling index (BLI) and transit through S phase (T_s) were determined and used to calculate tumour potential doubling time (T_{pot})

Median TLI (3·39 per cent, range 0·3–14·1 per cent) was similar to BLI (4·85 per cent, range 0·7–10·4 per cent). Although tumours with TLI values below the median were associated with a prolonged median disease-free interval (132 months) compared to high TLI cancers (85 months), and a 7 per cent survival advantage, Life table curves were not significantly different ($\chi^2=1{\cdot}16$, $P=0{\cdot}28$ for DFI; $\chi^2=0{\cdot}08$, $P=0{\cdot}78$ for survival). Median potential doubling time was 9·7 days (range 2·6–260 days) but its components BLI and T_s were not correlated ($r=0{\cdot}4$, $P=0{\cdot}11$) indicating they act as independent determinants of T_{pot}

We conclude that kinetic data provided by TLI is relatively limited which may explain its failure to predict long term outcome *In vivo* BrdU labelling adds a dynamic measurement of tumour kinetics whose prognostic value merits evaluation.

Effect of tamoxifen on bone mineral density

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Tamoxifen may protect against breast cancer by its anti-oestrogenic effects but little is known about its possible effects on human bone

Bone mineral density (BMD) was measured in 50 postmenopausal female patients treated with tamoxifen for at least 12 months. Each patient had surgery for primary breast carcinoma with no known recurrence or metastatic spread. All of the patients were assessed to exclude other causes of a change in BMD from normal BMD was assessed using single energy quantitative computed tomography (SE-QCT) and software (Siemens Osteo CT) This software contains a comparable set of control patients and it calculated the standard deviations from normal. An automized technique was used to analyse the second lumbar vertebra of each patient.

A one-sample T test indicated that there was a significant decrease in BMD in patients treated with tamoxifen ($P<0{\cdot}001$) There is also a non-significant decrease in BMD with time in the tamoxifen group ($t=1{\cdot}29$, df=48; $0{\cdot}10<P<0{\cdot}25$) Human osteoblasts are known to contain oestrogen receptors and our study suggests that tamoxifen is antioestrogenic at these sites making patients more prone to osteoporosis.

1. Kalendar WA, Felsenberg D, Louis O *et al.* Reference values for trabecular and cortical vertebral bone density in single and dual energy quantitative computed tomography. *Eur J Radiol* 1989; **9**: 75–80.

Late results of a randomized crossover study of mastectomy or tamoxifen in elderly patients with operable breast cancer

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We have previously reported the early results of 135 consecutive patients aged 70 or over with primary breast cancer prospectively randomized to receive either wedge mastectomy (simple mastectomy without undercutting of the flaps) or 20 mg tamoxifen b.d. as the initial treatment. Unlike other studies this one included only patients with operable breast cancer. Patients randomized to tamoxifen crossed over and had a wedge mastectomy if there was any sign of local progression. The criteria for entry were: age >70 years, operable breast cancer (maximum diameter 5 cm) and assessed fit for surgery. Patients randomized to wedge mastectomy were treated with further excision and/or radiotherapy for local recurrence and on failure of these treatments, or on diagnosis of metastatic disease by tamoxifen.

The mean time from randomization is now 65 months. There is still no significant difference in survival between the two groups. In the mastectomy and tamoxifen groups respectively, 18 and 15 patients have developed metastases with no difference in the time to metastases between the groups. The time to locoregional recurrence was significantly better in the mastectomy group compared to the time to locoregional progression in the tamoxifen group ($P=0{\cdot}0009$): at 5 years, 62 per cent of the mastectomy patients were locoregional recurrence-free compared to only 32 per cent of tamoxifen patients who had not shown locoregional progression.

This report supports our early results that mastectomy gives better locoregional control than tamoxifen alone and confirms our view that the optimum treatment in elderly patients, fit for surgery, with operable breast cancer includes mastectomy.

Comparison of cyclical sequential tamoxifen and megestrol acetate with tamoxifen alone in advanced breast cancer

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Short term tamoxifen therapy stimulates progesterone receptor synthesis in breast cancers, potentially rendering them more sensitive to subsequent progestogen therapy. A six weekly cyclical regimen of 20 mg tamoxifen daily for two weeks, 160 mg megestrol acetate daily for three weeks, then no treatment for one week has been evaluated in a prospective randomized controlled trial.

A total of 255 women received either continuous tamoxifen alone (group A, $n=124$) or cyclical therapy (group B, $n=131$) and the response assessed using WHO criteria (see *Table*)

	Group A	Group B
Response	Tamoxifen	Tamoxifen + megestrol acetate
Non-evaluable	4	1
Complete response	14 (11·7%)	18 (13·8%)
Partial response	29 (24·2%)	35 (26·9%)
Stable	25 (20·8%)	35 (26·9%)
Progression	52 (43·3%)	42 (32·3%)

The overall response was approximately equal in both groups (complete + partial response: group A = 35·8 per cent, group B = 40·8 per cent; $P=0{\cdot}505$) and there was no difference in median response duration in responders (group A = 128 weeks, group B = 131 weeks, $P=0{\cdot}711$). Median survival was longer in patients receiving cyclical therapy (group A = 92 weeks, group B = 134 weeks, $P=0{\cdot}015$) and the estimated relative death rate, group B/group A was 0·68 ($P=0{\cdot}025$).

In the absence of a difference in response rates, the improved survival of patients on cyclical therapy may be attributable to delayed progression in non-responders.

Proliferation of normal human breast tissue in nude mice after ovarian hormone stimulation

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Normal human breast tissue was implanted into intact female nude mice in order to determine the effects of oestrogen and progesterone on proliferation.

Xenografts were removed at intervals after implantation and the tissue processed for histology. Cellular proliferation was measured by thymidine labelling (TLI). Oestradiol levels (800–1500 pmol l^{-1}) or progesterone (38–54 nmol l^{-1}) were maintained at human luteal phase levels by subcutaneous silastic implants. Lobular architecture was maintained for at least 56 days in untreated animals. The TLI fell from 2·32 per cent ± 0·24, $n=52$ to 0·46 per cent ± 0·08, $n=34$ by 14 days after implantation. Administration of oestrogen after this time for 7 or 14 days increased the TLI to 2·24 per cent ± 0·15, $n=49$ and 2·70 per cent ± 0·23, $n=41$ respectively ($P<0{\cdot}005$). Grafts removed at daily intervals indicated an initial rise in TLI on day 3, 1·24 per cent ± 0·24, $n=14$ ($P<0{\cdot}05$). There was a dose-response effect of oestrogen on TLI. Seven or 14 days progesterone treatment failed to stimulate TLI above untreated control values, 0·53 per cent ± 0·09, $n=31$ (P = n.s.) The TLI after combined oestrogen and progesterone for two weeks was 2·45 per cent ± 0·44, $n=24$ versus 2·70 per cent ± 0·22, $n=26$ for oestrogen treatment alone (P = n.s.).

These experiments indicate that oestrogen rather than progesterone is the major ovarian hormone responsible for human mammary epithelial proliferation in this model system

Loss of a putative tumour suppressor gene from the long arm of chromosome 17 in human breast cancer

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Loss of tumour suppressor gene function is known to play a key role in the pathogenesis of human cancer. As a marker for tumour suppressor gene loss, we have examined allele loss from the long arm of chromosome 17 (17q) in breast cancer.

Dioxyribonucleic acid (DNA) was extracted from the peripheral blood lymphocyte and breast carcinoma tissue of 26 patients. Paired blood and tumour DNA samples were subjected to restriction endonuclease digestion, gel fractionated, the DNA fragments transferred to a nylon membrane by Southern blotting and the blots probed with the probe pTHH59 which identifies DNA from the tip of chromosome 17q.

Autoradiography demonstrated that 19 patients were constitutionally heterozygous (informative) and in the tumour DNA from 9 of these patients (48 per cent) allele loss was clearly demonstrated. There was no correlation between 17q allele loss and expression of the c-erbB-2 oncogene, also located on 17q, nor with a range of clinical and pathological parameters.

These data suggest, for the first time, that loss of a tumour suppressor gene from 17q occurs in a high proportion of human breast cancer.

Flow cytometric DNA histograms in primary breast cancer

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There are conflicting reports of DNA content alone (ploidy) in predicting prognosis in breast cancer. We have previously shown that this is only a weak prognostic factor[1].

In 400 consecutive primary breast cancers followed up from 9 to 14 years, on dissociated paraffin embedded material, DNA histograms have been analysed and DNA ploidy and cell cycle compartments quantified. Actuarial survival has been calculated and Mantel-Cox analysis applied.

Parameter	Correlation with survival	
	χ^2	*P* value
DNA aneuploidy	3·94 (1 d.f.)	<0·05
S phase fraction (SPF)	18·6 (2 d.f.)	<0·001
Proliferative index (PI)	20·48 (2 d.f.)	<0·001
Histogram type (DNA ploidy and SPF combined)	20·35 (2 d.f.)	<0·001

The best prognostic discrimination is obtained by the addition of SPF to ploidy. Low S-phase/diploids have 83 per cent survival at 5 years against 52 per cent for high S-phase/aneuploids.

Cell cycle components alone are predictors of survival in primary breast cancer The addition of these measurements to ploidy improves the prognostic power and provides the basis of an automated, objective system to replace histological grading.

1 Dowle CS, Owainati A, Robins A *et al.* Prognostic significance of the DNA content of human breast cancer *Br J Surg* 1987; **74** 133–6

Uncontrolled breast recurrence after conservative treatment for primary breast cancer: an avoidable problem

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Between November 1979 and December 1986, 263 patients were treated for primary breast cancer by local excision and radiotherapy. Local recurrence within the treated breast occurred in 56 patients; in 18 it was gross and uncontrollable and in 14 of these it occurred within 24 months of primary treatment. Analysis of clinicopathological features showed patient age, nodal status, tumour size and definite vascular invasion to be predictive of breast recurrence.

Conservative is now not advised if the tumour is >3 cm or there is mammographic evidence of extensive or multifocal disease Re-excision is advised if the excision margin is <5 mm and conversion to mastectomy is advised if the patient is under 50 years with vascular invasion.

A total of 184 patients have since been managed according to these new criteria, wiith a median follow-up of 18 months (range 2–38). Three (1·5 per cent) patients have developed ipsilateral breast recurrence.

By using the above criteria the early morbidity of gross and uncontrolled breast recurrence has been avoided.

Ulcerative colitis in the anal canal of patients undergoing restorative proctocolectomy

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It is common practice to leave the anal canal *in situ* in patients undergoing restorative proctocolectomy for ulcerative colitis. We studied the pathology specimens of 24 such patients to determine the incidence and severity of inflammation in the anal mucosa. In 12 patients who had a colectomy and mucosal proctectomy the rectal and anal mucosae were reviewed. In 12 patients the pouch was stapled onto the anal canal; in these the rectal mucosa and distal (anal) ring of tissue recovered from the stapling instrument were reviewed. Histological sections were graded in terms of architectural distortion, fibrosis, chronic inflammation in the lamina propria, crypt abscess formation, ulceration and dysplasia. Each feature was graded as absent (score = 0), mild (= 1), moderate (= 2) or severe (= 3).

The anal canal mucosa was inflamed in each patient and no significant difference could be demonstrated between the degrees of inflammation in their rectal and anal mucosae (mean scores 7·1 and 6·2 respectively in mucosal proctectomy cases; 6·8 and 6·3 respectively in stapled cases) In five patients (21 per cent) the inflammatory changes were more severe in the anal canal. We conclude that the anal canal is always involved in ulcerative colitis severe enough to require proctocolectomy

Reduction by myectomy of ileal motility after ileoanal anastomosis

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It has been suggested that myectomized ileum might form as good a 'neo-rectum' as the ileal J pouch. Ileo–anal anastomosis without a reservoir (IAA) yields poor functional results which are due in part to the high-pressure ileal contractions. Bowel content may stimulate ileal motility, perhaps by the effect of volatile fatty acids (VFA) present in the stool. Our hypotheses were that myectomy of the ileum would reduce its motility and that VFA elicit contraction of the ileum.

Twenty dogs were allotted randomly to undergo IAA alone ($n = 6$), IAA with ileal myectomy (M, $n = 8$) or IAA with J pouch (J, $n = 6$) Ileal motility was studied 8 months later in conscious dogs by means of four microtransducers. Intraluminal pressures were recorded for 45 min (period 1). Intermittent boluses of 15 ml VFA solution (66 per cent acetic, 24 per cent propionic, 10 per cent butyric acids) were then administered *per anum* at 5 min intervals for 30 min (period 2).

	IAA	M	J
Number of contractions (period 1)	58* (34–75)	8 (4–22)	15 (7–20)
Amplitude of contractions (mmHg)	80** (68–88)	53 (41–57)	55 (36–63)
Motility index (mmHg min)	600* (188–910)	80 (65–138)	122 (23–135)
Discrete clustered contractions per VFA instillation (period 2)	60%	60%	60%

Values are medians with interquartile range in parentheses. * *P* <0·01, ** *P* <0·05

Volatile fatty acids in physiological concentrations stimulated ileal contraction in each of the groups Myectomy reduced ileal motility significantly.

Bile acid absorption following restorative proctocolectomy

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Pouch formation with conversion of the terminal ileum to a reservoir may alter bile acid reabsorption by ileal mucosa. Most information on bile acid absorption is extrapolated from animal experimentation.

We have developed a technique to study bile acid kinetics in human ileal biopsies and used it to compare taurocholic acid (TCA) absorption in normal human ileum, pouch ileum and ileum from patients with ulcerative colitis with an intact colon and with end ileostomy.

Biopsies or tissue resected at surgery were mounted as isolated mucosa in a small flux chamber Krebs buffer (pH 7, 37°C) was added to each side of the membrane. After 45 min, incubation buffers and tissue were collected for analysis Using radiolabelled TCA, studies with normal mucosa have shown that active absorption is reliably and reproducibily demonstrated at concentrations at 10 μmol TCA. One unit of tissue uptake is equivalent to an uptake of 10 μmol TCA in $\mu g\ g^{-1}$ wet wt in 45 min Results are given as mean ±s.d..

Tissue uptake (units)		
Mucosa–serosa	Serosa–mucosa	With inhibitor NaF/ouabain
14·61±3·98	1·22±0·24	6·06±1·31

Comparing different clinical groups the following results are obtained.

			Ulcerative colitis	
	Normal	Pouch	intact colon	colectomy + ileostomy
No. of patients	8	8	4	4
No. of chambers	28	16	25	13
Uptake (units)	14 6±3·98	14·42±4·72	11·45±1 36	13·09±4·82

The active absorption of TCA in pouches is not significantly different from normal ileum or patients with an ileostomy This suggests that formation of a pouch *per se* does not adversely affect TCA absorption.

Optimal muscle configuration of the neoanal sphincter

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Studies suggest that a neoanal sphincter can be constructed by electrically stimulating the transposed gracilis muscle The optimal neosphincter configuration is not known. Four arrangements were studied in a rat model.

A resected segment of colon was attached to an infusion chamber and the detached gluteus maximus muscle then fashioned isometrically as a slit (S), a slit with a kink (SK), a split (SP) or a ring (R) to form a neosphincter that could be stimulated to tetany At constant volume of saline the tension of the inactivated muscle was adjusted until leakage of a continuous stream occurred After neosphincter activation, saline was infused until leakage occurred. The volume difference was measured and the muscle weighed.

Mean volumes for S, SK, SP and R at mean muscle weight were 254·6±24·7, 344·2±23·1, 327·0±23·0, and 383·5±25 8 ml, respectively ($F=4{\cdot}363$, $P<0\,025$). The volume retained increased with muscle weight for S (40 47 ml g^{-1}, $P=0\,03$) and SP (70·48 ml g^{-1}, $P=0{\cdot}001$) though not for SK and R. This suggests that the latter two retain more volume by virtue of their configuration mimicking the normal anorectal angle and external anal sphincter than their size. In our last 10 patients we have adopted an alpha loop configuration instead of the conventional gamma type to achieve a kink and a ring.

Relationship between rectal and duodenal polyposis in familial adenomatous polyposis

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Almost all patients with familial adenomatous polyposis (FAP) develop duodenal polyps, the severity of which is graded stage I (minor) to stage IV (major) Although only 10 per cent of patients have stage IV disease, regular endoscopy is recommended for all.

To test whether the development of severe duodenal polyposis could be predicted in another way, the status of the rectum was assessed in 81 FAP patients from a foregut screening programme. The fulguration ratio, defined as the number of rectal fulgurations performed divided by the number of years since colectomy, was used as the index of rectal polyp severity

	Stage of duodenal polyposis			
	I	II	III	IV
No. of patients	17	28	27	9
Fulguration ratio				
Median	0	0·13	0 23	0 4
Interquartile range	0–0·3	0–0·2	0·04–0 5	0·2–0·5

Although the fulguration ratio was significantly higher in stage IV than in stage I ($P<0\,02$) or stage II ($P<0\,03$) duodenal polyposis, the wide scatter of results means that rectal polyp severity should not be used as a guide to duodenal polyp severity in individual patients However, the group of FAP patients with severe duodenal polyposis also had severe rectal polyposis, suggesting that phenotypic expression in FAP may be determined by environmental factors

Mechanism of sphincter injury following low anterior resection

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Up to 25 per cent of patients have difficulty with incontinence following low anterior resection of the rectum. An important factor is the fall in resting anal pressure which follows the procedure. Intraoperative injury to the internal anal sphincter during transanal use of the stapling gun, or damage to its innervation during mobilization and transection of rectum are possible underlying mechanisms. The aim of this study was to assess the relative importance of each in reducing postoperative resting pressure. Fourteen female greyhound dogs were randomized into two equal groups. Group A ($n=7$) had a low stapled EEA anastomosis of rectum, whilst the control group B ($n=7$), underwent a hand sewn anastomosis. Pre- and postoperative resting anal pressures were measured using a microtransducer tipped catheter connected to a computer Resting pressures were significantly reduced following EEA anastomosis (mean, s.e.m.) before: 49(3) mmHg; after: 20(4) mmHg; $P<0{\cdot}01$ and handsewn anastomosis before: 46(4) mmHg; after· 35(4) mmHg, $P<0{\cdot}01$ There was a significant reduction ($P<0{\cdot}05$) in postoperative resting anal pressure in the EEA group when compared with the handsewn control. A reduction in resting pressure occurs following anterior resection, but a significantly greater reduction follows EEA compared with handsewn anastomosis. This suggests a direct injury to the internal anal sphincter through passage and manipulation of stapling gun and is an important factor in impairing anal sphincter function following anterior resection

Systemic endotoxaemia in experimental colitis and following treatment with oral lactulose

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Systemic endotoxaemia has been demonstrated in active inflammatory bowel disease (IBD) and correlates with disease activity. It is postulated that endotoxins are absorbed through the damaged intestinal mucosal barrier and systemic spillover occurs when hepatic capacity to eliminate portal endotoxins is exceeded. Systemic endotoxaemia may be responsible for the systemic clinical and laboratory disturbances of IBD. The aim was to develop an experimental model of of colitis and gut-derived systemic endotoxaemia and use it to assess anti-endotoxin therapy.

Systemic endotoxin concentrations were measured using a quantitative *Limulus* assay in rats, eight days after intracolonic instillation of trinitrobenzenesulphonic acid in 30 per cent ethanol (TNBS/E) or normal saline. The TNBS/E group received either intragastric lactulose or water for 72 h before assay The severity of the TNBS/E-induced colitis was assessed using a colon macroscopic score (CMS) Results are given as means±s e.

	Systemic endotoxin concentration (pg ml^{-1})	CMS
Intracolonic saline Control ($n=14$)	4 0±1·2	0·6±0·2
Intracolonic TNBS/E Water ($n=15$)	39·8±12·6**	4·2±0·6***
Intracolonic TNBS/E Lactulose ($n=16$)	6·7±1·6*	4·6±0·5***

Significance versus controls. * n.s.; ** $P=0{\cdot}02$; *** $P=0\,0001$ Water versus lactulose (endotoxin $P=0\,04$; CMS n s) (Mann–Whitney U test)

Systemic endotoxaemia has been demonstrated in a rat colitis model. Treatment with the anti-endotoxin agent lactulose produces significant reduction in endotoxaemia.

Colonic vascular ligation in low anterior resection of the rectum for carcinoma

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Consecutive patients ($n = 168$) undergoing low anterior resection of the rectum with total mesorectal excision were studied. The ascending left colic artery was selectively preserved in 64 cases and the inferior mesenteric artery was ligated flush with the aorta in 104 cases. The selection of the method of colonic vascular ligation was essentially random except when nodes were palpable at the origin of the inferior mesenteric artery or the ascending left colic artery was absent.

Clinically significant anastomotic leaks occurred in 4 (6 per cent) cases in which the ascending left colic artery was preserved and in 11 (10 per cent) cases undergoing flush aortic ligation ($P > 0{\cdot}25$) (n.s.). Logistic regression analysis confirmed this finding and showed a decreased leakage rate in the presence of a transverse colostomy ($P < 0{\cdot}02$) and when anastomosis was performed using mobilized splenic flexure rather than sigmoid colon ($P < 0{\cdot}02$).

Proportional hazard analysis showed that recurrence and death were unaffected by the method of colonic vascular ligation. Hazards of death and recurrence increased significantly with increasing Dukes' stage ($P < 0{\cdot}001$) and hazard of death increased significantly with increasing age at operation ($P < 0{\cdot}01$).

Flush aortic ligation in low anterior resection is easier than selective preservation of the ascending left colic artery and gives comparable results.

Effects of severe haemorrhage and reperfusion on collateral blood flow and portal pressure in the cirrhotic rat

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Approximately 30 per cent of patients with acute variceal haemorrhage are actively bleeding at the time of their diagnostic endoscopy. However, it is not known whether variceal bleeding persists despite massive haemorrhage or whether rebleeding is precipitated by resuscitation. The aim of this study was to investigate the effects of haemorrhage and reperfusion on portal pressure and collateral blood flow in cirrhotic rats.

Rats with dimethylnitrosamine-induced cirrhosis were bled at a constant rate from a femoral artery. Arterial blood and portal pressure were monitored continuously. Splanchnic and hepatic haemodynamics (microsphere technique) and arterial blood flow (consecutive intrasplenic injection of ^{99}Tc-methylene diphosphonate and ^{99}Tc-albumin microspheres) were measured before and after haemorrhage and following reperfusion.

Haemorrhage resulted in a significant decrease ($P < 0{\cdot}001$; Student's paired t test) in portal pressure ($12{\cdot}1 \pm 0{\cdot}31$ to $6{\cdot}4 \pm 0{\cdot}6$ mmHg) but collateral blood flow remained unchanged ($1{\cdot}3 \pm 0{\cdot}2$ to $1{\cdot}1 \pm 0{\cdot}2$ ml min^{-1}). Following reperfusion, portal pressure was returned to approximately prehaemorrhage levels ($11{\cdot}3 \pm 0{\cdot}6$ mmHg) but collateral blood flow was significantly reduced (0·53 ml min^{-1}).

The results of this study suggest that the maintenance of collateral blood flow after haemorrhage may occur for the persistent bleeding observed in some patients and that resuscitation does not contribute to early rebleeding.

Non-invasive assessment of portasystemic shunting with oral galactose

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Development of portosystemic shunting is a feature of cirrhosis. Quantitative assessment of shunting has been attempted previously, but the methods were invasive and have found little application.

We assessed the use of oral galactose as a test substance to measure functional portasystemic shunting in portal hypertensive (PHT) patients ($n = 8$) and controls without liver disease ($n = 6$). The area under the peripheral blood galactose appearance curve (AUC) was measured over 60 min following administration of 4 g galactose in 50 ml water orally. Galactose was then infused i.v. (40 mg min^{-1}) to measure systemic galactose clearance (Cl). Systemic availability (SA) of the oral dose (D) was calculated as $SA = (100 \times AUC \times Cl)D$. Adherence of galactose elimination to first-order kinetics was tested in volunteers ($n = 6$) by measuring clearance at two i.v. infusion rates (40 and 80 mg min^{-1}). A further test was performed by analysing the concentration curve produced by a 30 min i.v. infusion of 3·6 g galactose as if it were produced by an equivalent oral dose.

Mean(s.e.m.) SA in PHT patients (72·2(11·8) per cent) was significantly higher than in controls (13·6(2·6) per cent, $P < 0{\cdot}005$, Student's t test). Doubling the infusion rate did not significantly affect systemic galactose clearance (1871(70) *versus* 1813(63) ml min^{-1}). The SA of the simulated oral dose (108·7(3·8) per cent) was not significantly different from the expected value of 100 per cent. We conclude that the SA of oral galactose may provide a useful index of functional portasystemic shunting in liver disease and portal hypertension.

Tropic role of enteroglucagon in pancreatic adaptation to subtotal enterectomy

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Proximal small bowel resection (PSBR) causes pancreatic hyperplasia, presumably via a humoral mechanism. Although cholecystokinin can stimulate pancreatic growth, its proximal distribution in the gut makes it an unlikely intermediary after PSBR. The potential roles of neurotensin and enteroglucagon were studied, since these hormones are mainly secreted from ileum and proximal colon. Male Wistar rats ($n = 40$) weighing 200–250 g were randomized to receive 90 per cent PSBR or jejunal transection and resuture. Rats were killed at 1 week or 1 month, when plasma was obtained for hormone assay and the pancreas was excised for protein and nucleic acid measurement. PSBR increased circulating enteroglucagon levels by 108 per cent at 1 week ($P < 0{\cdot}001$) and by 82 per cent at 1 month ($P < 0{\cdot}005$); neurotension levels were unchanged. Pancreatic wet weight was 2 per cent greater at 1 week (n.s.) and 23 per cent greater at 1 month ($P < 0{\cdot}001$). Pancreatic hyperplasia at 1 week was shown by a 36 per cent increase in DNA content (3·05 versus 2·25 μg mg^{-1} pancreas: $P = 0{\cdot}02$) and a 51 per cent increase in RNA content (10·97 versus 7·26 μg mg^{-1} pancreas: $P = 0{\cdot}02$). By 1 month, nucleic acid increments were no longer significant, probably reflecting the 18 per cent decrease in body weight in rats with such an extensive enterectomy. Enteroglucagon (but not neurotensin) appears to be a pancreatotropic as well as an enterotropic hormone.

Is impaired reticuloendothelial phagocytosis during acute pancreatitis a non-specific response to sepsis?

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It has recently been shown that reticuloendothelial (RE) phagocytosis is impaired in patients with severe acute pancreatitis (AP), but it remains unclear whether the findings are specific to acute pancreatitis, or a non-specific consequence of an acute inflammatory illness.

Phagocytic activity of the RE system was investigated by measuring the half-life of ^{14}C radioactivity in plasma after an intravenous injection of [^{14}C]methyl trypsin (1 mg; 10 μCi). Eleven patients with acute pancreatitis were compared to eight patients with severe sepsis and six normal controls. The degree of sepsis was quantified using the APACHE II score. In each group separation using Sephadex G-200 showed that 95 per cent of ^{14}C-radioactivity eluted with α_2-macroglobulin-trypsin complexes.

	n		APACHE II (median)		^{14}C half-life (min) (median)
Normal controls	6		–		11·2
Sepsis	8	*$P = 0{\cdot}05$	13	*$P < 0{\cdot}01$	15·0
Pancreatitis	11		4		25·0

* Mann–Whitney U test

The clearance of [^{14}C]trypsin complexes from plasma in septic patients was similar to normal controls. Patients with AP had significantly delayed [^{14}C]trypsin clearance despite lower APACHE II scores. These data suggest that there is a specific impairment of RE function in acute pancreatitis.

Mechanism initiating the preduodenal phases of gallbladder emptying in man

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We have previously demonstrated that both sham feeding and gastric distension initiate gallbladder emptying (GBE) in man. In this study putative cholinergic and hormonal mechanisms for the GBE responses to these preduodenal stimuli were investigated. GBE was measured using ^{99}Tc^{m}-EHIDA scintigraphy. Initially the gallbladder response to sham feeding ($n=30$) and gastric distension ($n=9$) was observed in healthy volunteers. Putative cholinergic mechanisms were investigated by administration of atropine prior to sham feeding ($n=11$) and gastric distension ($n=7$), and by studying the GBE response in patients with vagotomy to sham feeding ($n=11$) and gastric distension ($n=9$). Cholecystokinin release following sham feeding and gastric distension was measured by radioimmunoassay using two specific antibodies (R15 and A2) and by bioassay. Gallbladder emptying occurred in 16 of 30 volunteers following sham feeding and 6 of 9 volunteers following gastric distension. Atropine completely abolished GBE in response to sham feeding ($P=0·0026$, Fisher exact test) and gastric distension ($P=0·0114$). Vagotomy did not significantly reduce GBE response to sham feeding ($P=0·1734$) or gastric distension ($P=0·6372$). Neither the specific radioimmunoassays nor the bioassay detected a rise in plasma cholecystokinin

These results suggest that a vagally independent neural reflex initiates the GBE response to preduodenal stimuli.

Gallstone recurrence following percutaneous cholecystolithotomy

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Percutaneous cholecystolithotomy (PCCL) is emerging as a new method for treating symptomatic gallstones[1] and may have advantages over other non-operative treatments such as extracorporeal shockwave lithotripsy and dissolution therapy. The risk of gallstone recurrence following PCCL is unknown.

Of the 182 patients assessed for non-operative treatment of gallstones, 141 (77 per cent) were suitable for PCCL. PCCL was the chosen option in 88 patients of whom 78 had successful clearance of the gallbladder as determined by endoscopic and radiological examination. Fifty-three patients have been assessed clinically following PCCL with a mean follow-up period of 8 months (range 3–24). Early stone recurrence rate and gallbladder function has been evaluated by ultrasound scanning pre- and post-fatty meal.

Of 53 patients, 36 (68 per cent) were asymptomatic, six had residual symptoms, five had minor non-specific abdominal symptoms unrelated to their pre-treatment symptoms and six (11 per cent) had persistent abdominal pain but were stone-free and had functioning gallbladders. Five patients have recurrent stones, three due to residual fragments and two to *de novo* formation. None of these patients are symptomatic.

Follow-up is continuing but the early results suggest that recurrent stone formation following PCCL is due to residual stones as well as *de novo* formation Both direct inspection of the gallbladder and radiological examination fail to adequately demonstrate residual fragments. Residual fragments may be amenable to dissolution with adjuvant bile acid therapy.

1. Kellett MJ, Wickham JEA, Russell RCG. Percutaneous cholecystolithotomy. *Br Med J* 1988; **296**: 453–5.

Analysis of the patients who failed to respond to combined gallstone lithotripsy and bile acid therapy

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Early results of gallstone lithotripsy (ESWL) combined with bile acid therapy (ODT) have been encouraging. However, few data exist about the patients who fail to respond to this new therapeutic modality. In this study we evaluated the stone characteristics of these patients such as size, number and chemical composition (cholesterol, CHO, and calcium bilirubinate, CaBil, of both stone interior and exterior). To date, eighteen patients (16 per cent) have undergone cholecystectomy following failed ESWL+ODT. Four of the failures were due to ESWL complications which included jaundice ($n=1$), pancreatitis ($n=1$), and acute cholecystitis ($n=2$). The remaining 14 patients had insignificant fragmentation (FF) or clearance of fragments (FC) following six treatment sessions and a follow-up of six months.

		Stone characteristics (mean ± s.e.m)		Composition (mean%)			
				Exterior		Interior	
Cause of failure	*n*	Number	Size	CHO	CaBil	CHO	CaBil
FF	8	1±0	3·0±0·25	45·8	45·9	65·1	34·9
FC	6	14±4·4	1·1±0·38	35·5	59·5	53·7	46·3

All the stones in the FF group were large solitary stones. In addition, their mean diameter was significantly larger than the stones in the group FC ($P<0·001$, Student's *t* test). There was no significant difference in CHO or CaBil concentration between the stones in group FF or group FC. However, the gallstones in the FC group had a high concentration of CaBil in both stone surface and core. This study demonstrates that stone fragmentation is dependent on stone size. However, fragment clearance seems to be dependent on the chemical composition of the stones.

Minimally invasive gallbladder surgery using a new instrument: the laparocholecystoscope

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Minimally invasive procedures for removal of gallbladder stones are under investigation. The laparocholecystoscope (LCS) is a sleeved endoscope that can be introduced into the abdomen through a 2·5 cm incision under direct vision, avoiding damage to other structures. Suction provides secure fixation to the gallbladder preventing bile leakage. Standard urological instruments are used for cholecystolithotomy, aided by ultrasonic or electrohydraulic lithotripsy.

The LCS has been evaluated in 9 patients and 16 cadavers. Cadaveric studies demonstrated that the gallbladder fundus was readily identified and the LCS easily applied. In seven patients the LCS was used before cholecystectomy. In each case the gallbladder was cleared of stones without difficulty. One patient, unsuitable for open surgery, had his stones removed through the LCS. A foley catheter was left *in situ* and removed after 7 days. He made an uneventful recovery. One patient had a small fibrosed gallbladder which was visualized but was unsuitable for access.

The LCS permits removal of gallbladder stones avoiding the risk of biliary leakage and damage to other structures which have been associated with ultrasound guided puncture.

Real-time colour Duplex scanning following sclerotherapy of the greater saphenous vein

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The Quantum colour real-time Duplex scanner was used to scan the greater saphenous vein (GSV) in 89 limbs of 55 patients to study the efficacy of prior GSV sclerotherapy. The GSV was insonated from the saphenofemoral junction to the knee to evaluate both reflux to a standardized 30 mmHg Valsalva manoeuvre and evidence of GSV obliteration by sclerotherapy. These data were correlated with the number of sclerosing injections employed (mean 1·8, range 1–6), time from the last injection (mean 27·5 months, range 3–55 months) and strength of injectate used (0·5 to 3 per cent Sotradecol (STD)). Of 89 injected limbs, 51 (57 per cent) demonstrated reflux through the saphenofemoral junction, and reflux down the more distal GSV was found in 67 of 89 injected limbs (75 per cent). GSV obliteration was noted in only 18 of 89 injected limbs (20 per cent); 2 were totally obliterated and 16 were partially obliterated. The GSV was obliterated in 6 per cent below a refluxing saphenofemoral junction and in 40 per cent below a non-refluxing junction. A GSV obliteration rate of 9 per cent was found with a refluxing GSV and 50 per cent in a non-refluxing GSV Superficial femoral vein reflux was identified in 11 of the 89 limbs (12·3 per cent) and in every case was associated with both saphenofemoral junction and GSV reflux. We noted a trend towards more successful results with more concentrated injectate (3 per cent STD). Of patients, 51 per cent reported improvement in symptoms We conclude that sclerotherapy of the GSV in the presence of saphenofemoral junction or GSV reflux is unlikely to remain successful in the long term These patients require control of the refluxing junction prior to sclerotherapy.

Analysis of lower limb vein segments by venography and Duplex Doppler

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A prospective study was undertaken in 65 patients (68 limbs) with suspected lower limb deep venous thrombosis (DVT). Both venography and Duplex Doppler ultrasound tests were performed on 64 limbs in the femoral and popliteal segments. The calf veins were not studied in all cases, as a strongly positive proximal scan determined treatment. Venography was contraindicated in four cases Both tests were performed independently in separate departments within 24 h of each other

All venograms were assessed blindly by a single consultant radiologist at the end of the study. Duplex results were documented at the time of scanning with a reassessment at the end of the study where the diagnosis was in doubt.

Segment	Total (n)	Duplex positive +V	Duplex positive −V	Duplex negative +V	Duplex negative −V	Accuracy (%)
Femoral	64	21	0	1	42	95 5 $P<0\ 01$
Popliteal	64	21	1	2	40	88·5 $P<0{\cdot}05$
Calf	49	17	3	4	25	70

+V, with venography; −V, no venography. Comparison of multiple proportions

Duplex ultrasound can identify DVT with a high degree of accuracy in the proximal venous segments of the lower limb, but accuracy falls as the examination proceeds distally. A negative scan excludes DVT with a high degree of confidence, and this test should now become the standard for diagnosing DVT with venography being reserved for those where suspicion is high and the scan result in doubt.

Deep vein reflux is reduced by compression of the venous foot pump

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Venous return from the leg has traditionally been regarded as being mainly due to the calf muscle pump Chronic venous insufficiency is due to a combination of venous reflux and a disordered calf muscle pump Gardner and Fox recently demonstrated a functionally significant venous plexus on the lateral side of the foot[1]. We have compared the degree of popliteal vein reflux following compression of the calf and foot muscle pumps in patients with proven deep venous insufficiency

Eleven patients with popliteal vein reflux detected by Duplex scanning were studied. An inflatable foot pump (A-V Impulse System, Novamedix, Andover, UK) was applied to the foot. The popliteal vein was then imaged continuously with the patient standing, using a 7 5 MHz transducer. Venous return was initiated by manual calf compression and then by activation of the foot pump which compresses the foot for a period of 3 s.

The Doppler sonograms resulting from each manoeuvre were recorded and photographed Images were then enlarged and the areas on the sonogram representing antegrade and retrograde flow were measured using a sonic digitizer. A reflux index (RI) was calculated for each sonogram, expressing retrograde flow as a percentage of antegrade flow.

	Reflux index (%)
Calf compression	65 (51·6–107 3)*
Foot compression	35 (26·4–62·8)*

Results are median with interquartile range in parentheses $^*P<0{\cdot}02$, Wilcoxon's paired test

These results indicate a significant reduction in deep vein reflux when venous return is initiated from the venous foot plexus rather than from the calf muscle pump This indicates that a disordered calf muscle pump may exacerbate reflux in patients with venous insufficiency and that increasing the proportion of venous return from the foot plexus may be beneficial A trial of the effect of regular foot compression on venous function in patients with chronic venous insufficiency is warranted

1. Gardner AMN, Fox RH. The venous pump of the human pump – preliminary report. *Bristol Medico-Chir J* 1983; **98** 109–12.

Prostaglandin E_1 in aortic surgery

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Pulmonary dysfunction is common after major surgery, and may be due to platelet and leucocyte activation with pulmonary sequestration Prostaglandin E_1 (PGE_1), a potent inhibitor of platelet aggregation may inhibit this process

Twenty patients undergoing elective aortic surgery were randomized to PGE_1 ($30\ ng\ kg^{-1}\ min^{-1}$) or normal saline by infusion during surgery. Platelet count, inferior vena caval microaggregate by screen filtration pressure (SFP), arterial partial pressure of oxygen (P_{aO_2}) and alveolar gas exchange (A_{aDO_2}) were measured over the perioperative period.

		Preop	Day 1	Day 7
Platelets	PGE_1	298±11·5	178±22 7	410±45 3
$\times 10^9$ per l	Control	293±26 3	169±22 7	315±44·5
P_{aO_2}/F_{IO_2}	PGE_1	400±22	318±15	363±20
(Ratio)	Control	423±15	288±23	342±21
A_{aDO_2}	PGE_1	24 1±4·1	45·5±8 8	33 9±3·8
(mmHg)	Control	19·6±2·9	63 9±19·6	59 4±23 5

F_{IO_2}, fraction of inspired oxygen

Microaggregates measured by SFP rose significantly to SFP 1 41 in controls whereas the rise in PGE_1 patients to 0·83 was not different to 0 82 preoperatively. Platelet count fell further and recovered slower in control patients (n s) Arterial oxygenation and alveolar gas exchange in control patients showed a significantly greater fall on the seventh day compared to preoperatively ($P<0{\cdot}01$).

There was a reduction in both intravascular microaggregate formation during surgery and the subsequent deterioration in pulmonary function in patients on PGE_1.

Colour coded Duplex sonography as a replacement for venography in the diagnosis of acute deep vein thrombosis

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Although grey scale Duplex sonography is accurate for detecting thrombi confined to the femoropopliteal veins, its value in demonstrating calf vein thrombi remains controversial because of the difficulty in visualizing these veins. Colour-coded Duplex sonography may overcome this disadvantage because colour helps in better identification of these veins and contained thrombus.

In this study 58 patients (60 limbs) who presented with clinical features of acute deep venous thrombosis were investigated both by ascending venography and Duplex sonography. The results which were analysed by independent observers in a blind manner are shown in the *Table*

Site of thrombus	No. detected Venography	Sonography
Axial and calf veins	22	16
Axial	13	11
Calf	21	15
Isolated axial	1	1
Isolated calf	9	5

Overall accuracy of Duplex sonography was 90 per cent, with positive predictive value of 100 per cent. However, the negative predictive value for proximal thrombosis was 82 per cent compared with 71 per cent for calf thrombosis alone.

These results indicate that even with recent modifications, colour Duplex sonography still misses 30 per cent of significant calf vein thrombosis

Evidence of a generalized fibrinolytic response of venous endothelium to localized thrombus

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The distribution of the vascular fibrinolytic response to thrombus and the messenger mechanism through which it is achieved have not been discovered. Using a thrombus model which preserves venous endothelium, occlusive laminated thrombi were raised in the infrarenal vena cava (IVC) of six rats. Ten control rats underwent IVC dissection and perfusion with Ringer's solution alone The thrombosed cava was excised at 6 days as well as the spleen, superior vena cava, and femoral veins The tissues were homogenized and resuspended in an acetate buffer and tissue plasminogen activator (tPA) content calculated using a bioimmunoassay[1]

	Mean(s.d.) tPA (units g^{-1}) IVC	SVC	Fem. V	Spleen	Thrombus
Thrombosed	154(27)	266(26)	176(66)	46(7)	12(4·5)
Controls	229(40)	220(34)	92(16)	48(8)	—
P (*t* test)	0 002	0.02	0·003	NS	—

At 6 days the tPA content of the vein wall in contact with the thrombus is significantly reduced compared with the controls. The veins at some distance from the thrombus contain significantly more tPA than the controls These findings suggests that occlusive thrombus directly inhibits tPA production in adjacent vein wall whilst increasing tPA synthesis in other veins through some as yet unknown messenger

1 Mahmoud-Alexandroni M, Heath AB, Gaffney PJ. Sensitive and direct assays for functionally active plasminogen activators (tissue-type and urokinase-type) in plasma *J Clin Pathol* 1989, **92**. 308–14.

Effect of blood flow on endothelial cell monolayers

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The potential benefits of endothelial cell seeding of vascular grafts depends not only on effective cell attachment but also on the ability of the cells to resist the stresses of blood flow We have investigated the effect of different flow rates on immediately (short) seeded grafts and also on monolayers of endothelial cells formed by incubating the grafts in a seeding chamber overnight (long). Endothelial cells were labelled with indium-111 oxine and seeded at 1×10^5 cells cm^{-2} onto 15 cm × 4 mm i.d fibronectin-coated ePTFE grafts. The grafts were seeded every 5 (short) or 20 (long) min with one of four cell aliquots and rotated 90° between each The short group was used at this point whereas the long group was incubated on a roller table overnight. Grafts were then exposed to flow rates of either 100 or 200 ml min^{-1} using heparinized blood. The results given are the percentage cell retention at designated time points (mean(s.d.))

Time (min)	Long 100 ml/min	Short	Long 200 ml/min	Short
10	93·7(2·1)	87·6(2·8*)	92·1(2 4)	68·4(17·0*)
30	90·1(2·7)	81·2(4 6*)	88·1(3·5)	59 3(16·6*)
60	86·9(3·5)	77 6(5·3*)	84 9(3 9)	53 6(16·3*)
120	83 7(4·4)	72 1(6·2*)	81 9(4·8)	49·9(15 7*)

* $P < 0·01$ within each flow group

s.e.m. of immediately seeded grafts showed scanty cell cover before and after flow. The long seeding procedure gave excellent cover with little change after flow In conclusion, seeding overnight produces a confluent cell lining, that resists the stresses of blood flow significantly better than the patchy cell covering produced by immediate seeding.

Objective assessment of the microcirculation in patients with venous disease

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It is thought that venous ulceration may be due to skin hypoxia. Currently held theories suggest mechanisms which might produce this[1]

In order to assess objectively the microcirculatory deficit in the skin of patients with venous disease, three tests of microcirculatory function have been employed. Transcutaneous oxygen ($P_{\mathrm{Tc,O_2}}$), laser Doppler velocimetry (LDV) and xenon-133 clearance have been measured The latter two parameters were assessed during reactive hyperaemia following a period of 3 min-ischaemia. This was achieved by inflating a below-knee tourniquet to 200 mmHg. Thirteen patients with liposclerotic skin and venous insufficiency proven on colour Duplex ultrasound scanning were studied and compared to 14 normal controls without venous or arterial disease. Measurements were made on the densest area of lipodermatosclerosis in the venous patients and on skin 5 cm above the medial malleolus in control subjects.

	$P_{\mathrm{Tc,O_2}}$ (leg/chest ratio)	Xe clearance (min) Skin	Fat	LDV Peak basal flow ratio	Time to peak (min)
Venous	0 425* (0 16–0 70)	2·24† (0 7–5 6)	14·1‡ (6 1–87 4)	2 4§ (1 5–2 9)	1 2¶ (1·0–1 9)
Controls	0 78* (0 63–0 85)	2 08† (1·1–4 0)	17·4‡ (7 6–36 1)	3 31§ (1 9–5 5)	1 5¶ (0 6–2 0)

Results are expressed as median with interquartile range in parentheses *†‡§¶NS, Mann–Whitney *U* test

No difference between the two groups was demonstrable for any of these parameters, although the $P_{\mathrm{Tc,O_2}}$ and the ratio of peak to basal LDV flow tended to be higher in the control group These findings do not support the presence of a microcirculatory deficit in patients with venous disease.

1. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982, **ii**. 243–5.

Abnormalities of muscularis mucosae in Hirschsprung's disease

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Structural abnormalities of muscularis musocae (MM) have recently been demonstrated in a mouse model of Hirschsprung's disease (HD) suggesting that an abnormal microenvironment may be a pathogenetic factor for HD. We aimed to verify these observations in HD patients

MM thickness in diagnostic rectal biopsies and resection specimens of six HD patients and six matched postmortem controls was measured histologically by two unbiased observers. Results were expressed as MM thickness values, and MM/muscularis externa ratios (MM/ME).

MM was consistently dysmorphic and invariably thicker in HD rectal biopsies: HD median 27·5 μm, range 12 0–42·5 μm; control median 8·7 μm, range 8·2–11·2 μm ($P\leqslant0{\cdot}001$). In resected HD specimens MM/ME was higher in aganglionic bowel (mean 0·54±0·001 s.e.) than ganglionic bowel (mean 0·026±0·001 s.e.) ($P\leqslant0{\cdot}001$). Compared to equivalent levels in normal control bowel, MM of HD patients was similar in distal aganglionic segment (MM/ME HD 0·055±0·001; control 0·057±0·006) but thinner in proximal ganglionic segment (MM/ME HD 0·026±0·001; control 0·043±0·001; $P\leqslant0{\cdot}001$).

Our findings support the 'microenvironment theory' of pathogenesis of HD and may have important practical implications on the use of superficial rectal biopsies for the diagnosis of HD.

Screen-detected malignant colorectal polyps

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In a controlled study of faecal occult blood screening for colorectal neoplasia, 120 invasive cancers have been detected following the investigation of positive Haemoccult tests. Twenty-eight (23·3 per cent) were polypoidal and were treated by endoscopic resection at colonoscopy, six subsequently underwent resection

Over the same period, 265 cancers were diagnosed in an age/sex-matched control group, only 9 (3·4 per cent) were treated by endoscopic resection ($\chi^2=40{\cdot}06$, $P<0{\cdot}001$), two of which underwent colectomy

All the screen-detected cancers were well/moderately differentiated Eleven (50 per cent) of those treated by endoscopy alone were larger than 2 cm, the remainder were between 1·0–1·9 cm Three arose in villous, 13 in tubulovillous and 2 in tubular adenomas, in 4 carcinoma completely replaced the polyp.

None of the six patiens requiring colectomy following endoscopic resection was subsequently shown to have residual tumour. Two patients, with possibly incomplete endoscopic resection, were not considered for surgery.

Eighteen patients in the screening group who underwent endoscopic treatment alone have been followed up for two years – all remain free of disease

A high proportion of screen-detected cancers are amenable to endoscopic resection, this is likely to reduce surgical morbidity and result in more cost-effective treatment

Obstructed urinary flow in patients with obstructed defaecation – pubo rectalis paradox?

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Patients with outlet obstruction constipation (OOC) have inappropriate contraction of the pubo rectalis on straining at stool and evidence of obstructed urinary flow during micturition. The mechanism producing these events is unknown.

We studied 10 consecutive patients with OOC by combined video-chain cystography and proctography. The position of the posterior pelvic floor (PPF), anorectal junction (ARJ) and vesicourethral junction (VUJ) were recorded along with anorectal (ARA) and posterior vesicourethral angles (VUA) Results were compared with historical controls.

The mean descent of the PPF, AJR and VUJ on micturition was 3·6±1 cm, 3·9±1·2 cm and 2·9±0·5 cm respectively (in controls these values were always <1 cm)

During attempted micturition the posterior VUA in controls opened from 95±10° to 128±12°, $P<0{\cdot}05$ In contrast, in patients with OOC the posterior VUA remained unchaged, 100±10° at rest and 97±9° on straining. The ARA remained closed with a mean of 93±5° at rest and 95±8° on straining

These results suggest that patients who fail to open the ARA during defaecation also fail to open their VUA during micturition A generalized pelvic floor disorder is postulated

Simultaneous dynamic integrated EMG proctography and cystometography

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The bladder and rectum share a common origin and work in harmony Disturbance of one may lead to a similar problem in the other. The two however have not previously been investigated dynamically and simultaneously.

A new system has been devised in which dynamic integrated pressure Emg (DIPE) proctography has been performed simultaneously with DIPE cystometrography in 25 patients (17 female and 8 male).

Of 16 patients with constipation, 10 had urinary voiding problems. Of these 10 patients 6 were unable to void urine at all during the study. Five of these six patients had either a rectocoele (1), anismus (1) or both (3). Four patients were only able to void urine by extreme abdominal straining (maximum voiding pessure 149·5 cmH$_2$O, range 140–162 cmH$_2$O). Three of them had anismus. Thus eight of ten patients with urinary voiding difficulty had a rectal abnormality which explained their urinary symptoms.

Similarly, of nine patients with idiopathic faecal incontinence eight were shown to have urinary incontinence Two had urge incontinence. Six had stress incontinence as demonstrated by bladder neck beaking and leak of urine on coughing. Three also had bladder neck descent on coughing, indicating pelvic floor dysfunction causing both their faecal and urinary symptoms

Thus this combined study showed that abnormalities in one system could explain similar symptoms arising in the other

Nucleolar organizer regions (NORs) predict dysplastic changes in ulcerative colitis

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Patients with ulcerative colitis have an increased risk of colonic cancer predicted by clinical features and histological findings such as dysplasia In colitis, histological changes are modified by the inflammatory process making diagnosis of dysplasia difficult. In addition absence of dysplasia fails to exclude cancer further limiting its diagnostic value. The aim of this study was to determine the diagnostic value of NORs (loops of ribosomal DNA reflecting cellular activity or malignant potential) in ulcerative colitis. We studied NOR counts in 25 patients (followed by colonoscopy and biopsy for 5–10, mean = 6·8 years) undergoing panproctocolectomy. Using a specific staining and counting technique multiple sections obtained prior to and following resection were studied. During follow-up no patient developed a carcinoma but six patients developed dysplastic changes with epithelial atypia, villous change and reduced epithelial mucous (NOR = 10±3) while six patients had changes similar to dysplasia but in the presence of inflammation (NOR = 5±2), $P<0{\cdot}05$ Mann–Whitney U test. Patients with inflammation alone (NOR = 3±1) had similar counts to normal values (NOR = 2±1). There was a progressive increase in NOR counts with duration of disease and values of (7±2) preceded onset of dysplasia by (1·1±0·6 years) In conclusion NORs may predict onset of dysplasia, detect dysplastic changes in the presence of inflammation and identify patients without suspicious histology who require close surveillance and early colectomy.

Changes in the defunctioned anorectum following Hartmann's operation

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Reversal of Hartmann's procedure may pose technical difficulties related to the rectal stump which can involute and be affected by diversion colitis. The aims of the study were to measure these changes. Six patients, three men and three women aged 56 (44–79) years were studied, five had Hartmann's procedure for complicated diverticular disease, one for carcinoma Sphincter manometry and proctometrography were measured one and three months postoperatively, diversion colitis was assessed endoscopically at three months[1]. Results were, at one and three months: sphincter length 3·0 (2·5–4·0) and 3·75 (2·5–4·0) cm, $P=$NS, maximum resting pressure 85 (70–103) and 110 (53–130) cmH$_2$O, $P=$NS; maximum squeeze pressure 185 (151–423) and 176 (135–360) cmH$_2$O, $P=$NS. Proctometrography: first sensation 30·5 (25–97) and 35 (30–88) ml, $P=$NS; maximum tolerable volume 186 (122–210) and 145 (80–151) ml, $P<0{\cdot}05^*$; maximum tolerable pressure 68 (40–90) and 53 (40–80) cmH$_2$O, $P=$NS.Endoscopic index of colitis· erythema 1 (0–2); oedema 1 (0–1); friability 0 (0–1); granularity 1 (0–2) and erosions 0 (0–1). Three months after defunction the anal sphincters and rectal sensation remain unaffected Despite only minor changes of diversion colitis rectal volume has decreased by a mean 40 per cent. This may account for some of the difficulties of the reversal procedure

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* Wilcoxon matched-pairs signed-ranks tests

1 Harig JM, Soergel KH, Komorowski RA and Wood CM. Treatment of diversion colitis with short-chain fatty acid irrigation. *N Engl J Med* 1989; **320**: 23–8

Pattern of cyclic AMP binding protein expression in colorectal cancer and benign mucosa

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Cyclic AMP (cAMP) exerts its effects through activation of protein kinase A (PK-A). The regulatory units (R) of PK-A bind cAMP and exist as two forms, RI (M_r 47–50 kDa) and RII (M_r 50–54 kDa).

Using a 8-[^{32}P]azido-cAMP photoaffinity labelling technique followed by polyacrylamide gel electrophoresis, cAMP binding proteins were identified in the cytosols of 17 paired colorectal cancers and related mucosa. The relative expression of each as a percentage was then determined by laser densitometry.

Three cAMP binding proteins of molecular weight 52, 50 and 47 kDa were identified and termed R52, R50 and R47 respectively. R47 (RI) is relatively overexpressed in cancer tissue ($n=17$, 55·9±s.e. 4·1 per cent) compared with related benign mucosa (44·7±1·9 per cent) ($P<0·005$ by paired t-test). R52 is virtually absent and R50 underexpressed in cancer compared with benign mucosa. We postulate that R52 and R50 are, respectively, the autophosphorlyated (activated) and de-phosphorlyated forms of RII.

This is the first report of RI overexpression in human colorectal cancer although it has been previously described in human colorectal cancer cell lines. Treatment of cell lines with cAMP analogues causes overexpression of RII, inhibition of growth and promotion of differentiation. Thus cAMP analogues may prove to be of value in the treatment of colorectal cancer.

Necessity of draining colonic anastomoses

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Is it necessary to drain colonic anastomoses? The majority of surgeons continue to routinely employ intraperitoneal drains following colonic surgery despite evidence to suggest increased morbidity associated with drains and the absence of any proven value. We have evaluated the use of drains in this group in a prospective randomized study in which patients were randomized to three groups: group 1 had no drain, group 2 had a closed suction drain for three days and group 3 had a closed suction drain for seven days Anastomotic integrity and the presence of intra-abdominal fluid collections were assessed by ultrasound on the third and seventh postoperative days All left-sided anastomoses were assessed by gastrografin enema on the seventh postoperative day.

A total of 62 patients entered the study. The groups were well matched for age, sex, diagnosis and site of colonic anastomosis. The results are shown in the *Table*

	Group 1	Group 2	Group 3
No. of patients	20	21	21
Operation			
Right colon	6	8	9
Left colon	9	8	7
Anterior res.	5	5	5
Hospital stay (days)	13 0±2·1	14·8±2·6	15·8±2 8
Wound sepsis	2	4	5
Radiological leak	2	2	2
Clinical leak	1	1	1
Fluid collection on ultrasound	2	3	0

The results of this ongoing study do not justify the routine use of drains after colonic surgery Such drains do not influence the fate of intra-abdominal fluid collection.

Neutrophil hypochlorous acid production and histamine inhibition in porcine ARDS

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Hypochlorous acid (HOCl), a long-acting neutrophil (PMN) oxidant, is associated with pulmonary dysfunction in adult respiratory distress syndrome (ARDS). An effective treatment of ARDS in swine is combined histamine and cyclooxygenase blockade using ibuprofen (I), cimetidine (C), an H_2-inhibitor and diphenhydramine (D), an H_1 inhibitor. However C reverses histamine inhibition of PMN oxidant generation, thus its use in such therapy is questionable. To study this problem we assessed neutrophil HOCl generation in four groups of anaesthetized pigs ($F_{IO_2}=0·5$, positive end expiratory pressure = 5 cmH$_2$O). Control animals (Con, $n=6$) received 0·9 per cent NaCl, septic animals (Ps, $n=8$) received live *Pseudomonas aeruginosa* 5 × 10^8 c.f.u. ml^{-1} at 0 3 ml 20 kg^{-1} min^{-1} for 1 h i.v. Treatment groups in addition to Ps received I, 12·5 mg kg^{-1} (Ps+I, $n=5$) or the combination of I (12·5 mg kg^{-1}), C (7·5 mg kg^{-1}), and D (10 mg kg^{-1}), Ps+CID, $n=6$) at zero and 120 min. Parameters of pulmonary function were measured; extravascular lung water (LW), arterial oxygen tension (P_{aO_2}) and static lung compliance (C_L). Peripheral blood PMN were isolated at 0 and 300 min and HOCl production was assayed (5-thio-2-nitrobenzoic acid oxidation).

	Baseline	Con-5 h	Ps-5 h	Ps+I-5 h	Ps+CID-5 h
P_{aO_2} (torr)	218±21	255±11*	98±13†	121±31†	213±26*‡
LW (ml kg^{-1})	6·7±0 9	7·0±0·8*	14·5±2†	8 9±1*	10·0±1
C_L (ml cm^{-1} kg^{-1})	1 6±0 2	1 5±0 1*	0 6±0 1†	1 4±0 2*	1 0±0 1†
HOCl (nmol)	9 6±0 3	9 5±0·4*	13 0±0·3*	10 1±0 1*	13 9±0·4†‡

* $P<0\ 05$ versus Ps-5 h; † $P<0\ 05$ versus baseline, ‡ $P<0·01$ versus PS+I−5h

Addition of H_1 and H_2 inhibitors to ibuprofen resulted in the loss of the protective down regulation on HOCl production, an increase in LW and a drop in C_L. These data support the concept of reversal of histamine inhibition of PMN oxidant generation by cimetidine.

Effect of endothelial cell cytoskeletal enhancement on lung permeability after remote tissue ischaemia

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Reperfusion of ischaemic tissue produces a thromboxane(Tx)-dependent lung injury characterized by neutrophil accumulation and increased microvascular permeability. Tx may promote vascular permeability by disrupting the actin microfilament cytoskeleton of pulmonary endothelial cells (EC). The effect of the plant cytokine phalloidin, which stabilizes the EC cytoskeleton *in vitro*, was studied. Phalloidin was infused at 0·25 mg kg^{-1} h^{-1}, 30 min prior to and during reperfusion, in 34 rats following 4 h of bilateral hindlimb tourniquet ischaemia. At 5 min and 4 h of reperfusion, plasma TxB$_2$ (pg ml^{-1}), pulmonary neutrophil accumulation (PMN/20 high power fields), lung water (wet to dry weight ratio) and pulmonary microvascular permeability (Evans Blue dye/albumin conjugate leakage, EB units) were measured Sham animals did not undergo ischaemia.

	Plasma TxB$_2$		EB units	Lung water	PMN
	5 min	4 h	5 min	4 h	4 h
Sham ($n=20$)	515±220	484±182	10±3	4·1±0 1	58±15
Saline ($n=28$)	2372±788*	3100±615*	117±17*	5 0±0 2*	108±15*
Phalloidin ($n=34$)	2572±814*	2937±548*	13±6	4 2±0 1	126±21*

* $P<0\ 05$ relative to sham, ANOVA

Phalloidin treatment of ischaemic animals did not affect TxB_2 production or pulmonary histology but prevented the increase in microvascular permeability and subsequent accumulation of lung water. Phalloidin treatment of sham animals did not alter baseline TxB_2, pulmonary histology or lung water. Pulmonary injury following peripheral tissue ischaemia is prevented by phalloidin, by a mechanism possibly related to preservation of the actin microfilament cytoskeleton of pulmonary EC.

Fibronectin, complement and plasma proteins during major survery

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Major surgery is associated with complement activation and reticuloendothelial dysfunction. The potential role of prostaglandin E_1 (PGE_1), which has potent vasoactive and cellular actions, was investigated in an animal model of major surgery and changes in plasma fibronectin concentration, complement activation and plasma protein concentration determined.

Twenty four pigs were randomized to receive either peroperative PGE_1 (100 ng kg^{-1} min^{-1}) or an equivalent volume of normal saline as controls. Animals underwent standardized aortic surgery with a controlled period of hypotension. Serial blood samples were taken during surgery and on the third postoperative day. Fibronectin was determined by a microELISA technique, total haemolytic complement activity (THC) by kinetic turbidimetry and plasma proteins by dye-binding assay

Fibronectin fell in both groups but the fall in untreated animals was significantly greater than in PGE_1-treated animals (48·5 compared to 26·18 per cent; $P<0·01$, Wilcoxon) There was evidence of increased capillary permeability Untreated animals showed a significantly greater fall in total protein (12·43 compared to 5·18 g dl^{-1}, $P<0·02$) and plasma albumin (11·16 to 5·55 g dl^{-1}, $P<0·001$) THC was unaffected by PGE_1 with both groups showing a fall towards the end of surgery due to complement consumption, and later an acute phase increase

Prostaglandin E_1 exerted a beneficial effect on fibronectin consumption and protein loss during experimental aortic surgery

Value of preoperative Lugol's iodine in patients with treated thyrotoxicosis

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Established practice has been to prepare patients undergoing thyroidectomy for thyrotoxicosis with Lugol's iodine to render the thyroid gland less friable but this practice has been questioned[1].

We have performed a prospective, randomized, double blind, placebo-controlled trial of preoperative Lugol's iodine on 22 patients (4 male). All patients were euthyroid on anti-thyroid drugs and received preoperative propranolol therapy A single surgeon (AR) performed all operations with intraoperative measurement of gland elasticity using a Swan-Ganz catheter technique. The results are summarized in the *Table*

	Mean age (years)	Mean blood loss (ml g^{-1} goitre)	Gland elasticity (mmHg ml^{-1})	Number of rebleeds	Number of tracheostomies
Lugol's iodine ($n=11$)	30·2	6·4	56	0	0
Placebo ($n=11$)	36·6	11·1*	38	1	1

* $P=0·005$ for difference to Lugol's iodine group (Student's t-test)

The significant reduction in blood loss per gram of organ excised and absence of major complications in the Lugol's iodine patients suggest that the routine use of preooperative Lugol's iodine is necessary There was not a significantly reduction in gland friability as measured by gland elasticity

1 Coyle PJ, Mitchell JE Thyroidectomy is Lugol's iodine necessary? *Ann R Coll Surg Engl* 1982, **64**: 334–5.

Effects of IGF-1 infusion on protein metabolism

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The insulin-like growth factors mediate the protein anabolic actions of growth hormones. As growth hormone administration has been demonstrated to improve nitrogen balance in septic and trauma patients, we wished to investigate the effects of IGF infusion on protein metabolism

We used infusion of [^{14}C]leucine, [^{15}N]urea and [6-^3H]glucose to measure metabolic responses during 5 h hormone infusions in fasted lambs. Three hormone infusions were compared. high dose IGF-I (50 μg kg^{-1} h^{-1}, $n=6$), which reduced plasma glucose concentration by 40 per cent, low dose IGF-I (15 μg kg^{-1} h^{-1}, $n=4$) which had no effect on glucose kinetics and an insulin dose which reduced plasma glucose concentration by the same extent as the high dose IGF-I (0·025 units kg^{-1} h^{-1}, $n=4$). Six controls were infused with saline.

Urea appearance was reduced significantly following high and low dose IGF-I infusions and insulin infusion by 12, 10 and 11 per cent respectively. High dose IGF-I infusion increased the fractional rate of protein synthesis in adductor and psoas muscle and liver tissue, and more than doubled the diaphragmatic and cardiac muscle fractional synthesis rate (FSR). Following insulin infusion, only cardiac FSR was significantly increased

We conclude that IGF-I reduces protein loss, and can do so at a dose which does not affect glucose metabolism. High dose IGF-I infusion stimulates protein synthesis IGF-I may have clinical potential in the nutritional support of severely ill surgical patients

Effect of platelet-derived growth factor on steroid-impaired healing intestinal wounds

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Platelet-derived growth factor (PDGF) accelerates the gain in tensile strength of healing incisional skin wounds[1]. Wound failure is more serious in intestine and more likely if healing is impaired There are few studies of the effects of steroids on healing intestine. Twelve pigs were divided into two groups, half were treated with betamethasone (12 mg/50 kg, twice daily), half with saline, beginning 48 h preoperatively and continuing until being killed at seven days. Animals underwent laparotomy, multiple ileal (three) and colonic (two) longitudinal enterotomy wounds were constructed at standard sites Healing was assessed by tensiometry. Breaking loads of steroid treated wounds were significantly lower ($P<0·01$ Wilcoxon rank sum test) in both ileum (158 versus 317 g cm^{-1}) and colon (199·5 versus 390 g cm^{-1}) A further six steroid treated pigs underwent operation, three sets of paired incisions (two ileal one colonic) were constructed at standard sites. Into each of a pair of incisions was placed either 20 μg of recombinant PDGF in a collagen vehicle or collagen alone. PDGF decreased breaking loads of both ileal (179 versus 239 g cm^{-1}) and colonic wounds (221 versus 235 g cm^{-1}) compared to a collagen control, neither result was significant at the 5 per cent level although the result for ileal wounds approached significance. PDGF does not accelerate healing in steroid impaired intestinal wounds and may even be detrimental.

1. Pierce GF, Mustoe TA, Senior RM, Reed J, Griffen GL, Thomasen A and Deuel T *In vivo* incisional wounds healing augmented by platelet derived growth factor and recombinant c-sis gene homodimeric proteins *J Exp Med* 1988; **167**· 974–87

Delivery of high osmolality intravenous nutrition peripherally via an ultra fine-bore silicone catheter: a randomized study

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Intravenous nutrition (IVN) can be administered via a peripheral vein but constraints upon osmolality require a feed which is deficient in carbohydrate. An ultra-fine silicone catheter (23 Fr) permits normal blood flow in the vein to be maintained and avoids occlusion and trauma to the vein. An ultra fine-bore catheter was compared to a conventional Teflon® (DuPont) cannula for delivery of a feed consisting of 1800 kCal daily, 80 kCal as glucose and 13 g of amino-acid nitrogen

Patients were randomized, and heparin (500 units l^{-1}) and hydrocortisone (5 mg l^{-1}) were added to all feeds.

	Ultra fine-bore silicone catheter	Teflon cannula
No of patients	15	12
Days of IVN (median)	5	5·5
No. of episodes of thrombophlebitis	1*	23
Median life of cannula (h)	128·5**	39

* $P<0{\cdot}002$, χ^2 test; ** $P<0{\cdot}001$, Mann–Whitney U test

These results suggest that ultra fine-bore silicone catheters can be used to deliver IVN with an osmolality of 1250 mOsm l^{-1} via a peripheral vein with a very low incidence of thrombophlebitis. Thus the dangers of central venous catheterization can be avoided in the majority of patients who require IVN.

Protein-calorie malnutrition impairs macrophage response to septic challenge

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Protein-calorie malnutrition (PCM) induces immunosuppression that predisposes to sepsis, but the mechanisms are unclear. This study examines the macrophage (MO) response to septic challenge in the malnourished host. One hundred and sixty mice (CFW/C3H-HEN) were randomly allocated to either control (24 per cent casein diet) or low protein (2·5 per cent casein diet) for eight weeks. The ability of two populations of MO, peritoneal MO (PMO) and Kupffer cells (KC), to respond (superoxide anion, O_2^-) to *in vivo* endotoxin challenge (LPS, 30 μg i.p.) and to *in vitro Candida albicans* (CA) challenge (per cent CA killing at 3 h, CAK, was measured). Antigen presenting cell function (APC, conalbumin using D.10 T helper cell line) was also assessed. PCM mice demonstrated decreased weight and cell yields. O_2^- production in resident and LPS-primed MO was reduced CAK was also significantly decreased in the PCM group as was APC function (control = 4563 ± 690 versus PCM = 2240 ± 177 counts min^{-1}*). Interferon gamma (γ-IFN, 100 U/10^6 cells) upregulated MO microbicidal activity (O_2^-, CAK) in the PCM group.

		PMO		KC	
		24%	2·5%	24%	2·5%
O_2^-	Res	92(±10)	55(±4)*	6(±1)	2(±1)
	LPS	333(±36)	175(±31)*	17(±6)	4(±0)
	γ-IFN	274(±64)	184(±28)	15(±2)	3(±3)
CAK	Res	25(±3)	14(±1)*	6(±1)	1(±0)*
	γ-IFN	36(±1)	21(±2)**	13(±1)	6(±1)*

* $P<0{\cdot}05$; ** $P<0{\cdot}01$ unpaired t test. Values expressed ±s.e.m.

Prolonged PCM significantly impaired the MO response to acute (LPS) and chronic (CA) septic challenge and the ability to present foreign antigen, critical to initiation of the immune response. Enhancement of microbicidal function by γ-IFN suggests a therapeutic potential for this lymphokine in the malnourished septic host.

Ability of non-invasive impedance analysis to predict 'at risk' femorodistal vein grafts

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Computer assisted impedance analysis is a newly developed technique to identify femorodistal/popliteal (FDP) vein graft and run-off stenoses. Pulsatile flow is measured using a standardized 8 MHz Doppler probe A pulse volume recorder measures pulsatile pressure. Transfer analysis is performed on the paired Doppler/pulse volume recorder signals and an impedance score derived[1].

Using intra-arterial digital subtraction arteriography (IA DSA) as the gold standard, analysis of 50 FDP grafts revealed significantly increased impedance scores in the 'at risk' group viz graft or run-off stenoses >50 per cent, 0·58 (0·43–0·72)*, when compared with the controls viz no stenoses, 0·34 (0·30–0·38), $P<0{\cdot}001$*. An impedance score of >0·45 was able to detect 20 of 22 stenoses, including six lesions in grafts with normal postexercise ankle pressures.

This score was then applied prospectively to graft surveillance in a further 57 FDP bypasses. Of 34 lesions, 33 were successfully predicted and confirmed on IA DSA. Similarly, impedance scores were significantly higher in the 'at risk' limbs, 0·56 (0·44–0·68)*, when compared with the controls, 0·38 (0·35–0·41), $P<0{\cdot}001$*. Of the 'at risk' grafts, 12 had subsequently failed and 7 stenoses have been repaired, impedance scores falling to normal in each graft.

Computer assisted impedance analysis is a sensitive predictor of FDP graft function and can detect both graft and run-off stenoses prior to failure. This test is non-invasive and is now used routinely for graft surveillance in our vascular laboratory.

*Means with 95% confidence limits in parentheses; Mann–Whitney U test

1. Wyatt MG, Muir RM, Tennant WG *et al.* Computer assisted impedance analysis (CAIA). A new method to detect 'at risk' femoro-distal grafts. Association of Surgeons of Great Britain and Ireland, Programme and Abstracts 1990; 96.

Lipodermatosclerosis and an oxygen diffusion barrier

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It is postulated that skin damage in patients with venous insufficiency is due to hypoxia, as the result of an oxygen diffusion barrier caused by pericapillary fibrin cuffs. There is little direct evidence to indicate that the diffusion of oxygen is actually impaired. We have investigated the clearance rate of xenon-133 from the skin and subcutaneous tissues in patients with liposclerotic skin and in normal controls This test reflects diffusion of the isotope across the skin into the microcirculation. Xenon has diffusion characteristics comparable to oxygen.

Eleven patients with venous insufficiency proven on Duplex ultrasound scan, and fourteen normal controls without venous or arterial disease underwent xenon-133 clearance measurements using the epicutaneous labelling technique described by Sjerson[1]. Clearance was measured under maximally hyperaemic conditions induced by 3 min of tourniquet ischaemia. Scintillation counts were collected for 20 min after tourniquet release. The resulting biphasic graph allowed clearance rates from skin and fat to be calculated by a computerized curve stripping technique.

	Skin clearance half-time (min)	Fat clearance half-time (min)
Venous disease	2·2 (0·7–5·6)	14·1 (6·1–87·4)
Normal controls	2·1 (1·1–4·0)	17·4 (7·6–36·1)

Results are expressed as median with interquartile range in parentheses

These differences are not significant using a Mann–Whitney U test. Xenon is a molecule four times larger than oxygen, yet it appears to diffuse across the epidermis and be removed by the skin microcirculation as efficiently in liposclerotic skin as in normal skin. We suggest that this mitigates against the presence of an oxygen diffusion barrier in lipodermatosclerosis.

1. Sjerson P. Blood flow in cutaneous tissue in man studied by washout of radioactive xenon. *Circ Res* 1969; **25**: 215–29

Role of echocardiography prior to peripheral arterial thrombolysis

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Left heart thrombus may contraindicate thrombolysis of peripheral arterial occlusions because of the risk of systemic embolisation.

Furthermore, the presence of a left heart thrombus might suggest embolism as the cause of occlusion, and hence embolectomy may be preferred. In this study we have evaluated the role of echocardiography in the cardiac assessment of patients prior to thrombolysis.

Fifty-one patients underwent clinical assessment, ECG and echocardiography prior to thrombolysis. High risk patients were those in whom a left ventricular thrombus was seen or who had mitral valve disease with atrial fibrillation.

Ten high risk patients were identified, three of whom had no cardiac history or ECG abnormality, three (30 per cent) high risk and five (12 per cent) other patients had embolic arterial occlusions. Echocardiography was essential in making the diagnosis in one case. Thrombolysis was successful in all eight patients with embolus. There have been no proven embolic complications in the ten high risk patients.

In conclusion, echocardiography should be performed on all patients prior to thrombolysis if left heart thrombi are to be detected, and may aid in distinguishing between embolus and thrombus. However, embolic occlusions appear to do well with thrombolysis and the risks of thrombolysis in these patients appears to be low.

Non-invasive assessment of the pedal arch prior to femorodistal bypass

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In patients with critical ischaemia, pedal arch patency is an important factor for successful femoropopliteal or distal (FPD) bypass, but is frequently underestimated with pre-operative arteriography. Pulse generated run-off (PGR) is a new method which can show the patency of the pedal arch, in addition to the integrity of its feeding calf vessels[1]

PGR was performed pre-operatively in 42 patients undergoing FPD bypass for critical ischaemia and compared with pre- and postreconstruction intra-arterial digital subtraction arteriograms (IA DSA). For each investigation, the number of calf vessels in continuity with the pedal arch was scored as 2, 1 or zero (maximum two vessels) and the pedal arch as complete (2), incomplete (1) or occluded (0).

There was no correlation between the pre-operative IA DSA and PGR. There was, however, an excellent correlation between the preoperative PGR and the postoperative IA DSA, for both calf vessel continuity at the ankle ($r_s = 0{\cdot}71$, $P < 0{\cdot}001$*) and for pedal arch patency ($r_s = 0{\cdot}79$, $P < 0{\cdot}001$*).

These results show the value of PGR in the assessment of both feeding vessel and pedal arch patency, and confirm the inadequacy of pre-operative arteriography. The study has resulted in bypasses being contemplated in situations previously regarded as unreconstructable, and in choosing the vessel for distal anastomosis with the best run-off into the pedal arch.

* Spearman rank correlation

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Flow augmentation of tibioperoneal veins by simultaneous use of an AVI foot pump during coloured Duplex sonography

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The functional and anatomical abnormalities in the calf deep venous system of the patients suffering from chronic venous insufficiency are poorly understood. Venography, which is the standard method used to visualize deep veins, frequently fails to demonstrate the three pairs of tibioperoneal veins. Although coloured Duplex sonography with recent modifications is excellent in demonstrating the proximal axial veins, all the calf veins are not visualized because of low venous flow rate. A recently developed foot pump, using an arterial venous impulse (AVI) system, has been shown to augment flow in tibial veins.

In this study, both the coloured Duplex sonography and AVI foot pump were used simultaneously to visualize tibioperoneal vessels in 86 limbs. A pneumatic pad applied to the sole of the foot was inflated for 3 s by spontaneous activation impulse system and the cycle repeated every 20 s. All the three pairs of tibial veins were visualized in 80 out of 86 limbs. In six limbs, flow augmentation demonstrated venous occlusion due to previous thrombosis. Deep venous reflux was assessed by Duplex sonography and foot volumetry in another 66 limbs. Reflux was quantified by spectral analysis. Both tests correctly identified venous reflux in 90 per cent of limbs. However foot volumetry missed 10 per cent of limbs shown to have reflux on sonography.

The results indicate that combined use of AVI foot pump and colour Duplex sonography provides an accurate method for assessment of deep venous system and reflux in the proximal axial veins.

Cerebrovascular symptoms and type of CT scan infarcts

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It has been suggested that a large number of patients (30 per cent) with hemispheric transient ischaemic attacks (TIAs) or amaurosis fugax (AF) and internal carotid artery stenosis have silent cerebral infarcts on CT brain scanning. However, there is little information about the type and site of infarction. The purpose of our study was to determine the difference between infarcts in patients with stroke, TIAs and AF.

Of patients referred for Duplex scanning, 383 were studied with CT brain scan. 142 had a hemispheric stroke with maximum recovery, 133 had TIAs and 65 had AF. CT scan infarcts were classified as shown in the *Table*.

Type of lesion on CT scan	Presentation of symptomatic hemisphere Stroke ($n = 149$)	TIAs ($n = 155$)	AF ($n = 73$)
Watershed	18(12%)*	6(4%)	0
Discrete subcortical	19(13%)	22(14%)*	2(3%)
Large cortical	29(19%)*	6(4%)	1(1%)
Small cortical	11(7%)	6(4%)	3(4%)
Basal ganglia	21(14%)*	8(5%)	3(4%)

* $P < 0{\cdot}01$

The results indicate that patients with hemispheric TIAs have a lower incidence of watershed and large cortical infarcts than patients with stroke. Patients with AF do not have watershed infarcts. They have a lower incidence of discrete subcortical infarcts. It may mean that AF emboli tend to be confined to the retina or they are too small to produce large silent CT scan infarcts. This hypothesis also explains why the incidence of subsequent stroke in patients with AF is lower than patients with TIAs.

Modification by LAK cells of the effect of interleukin 2 on delayed type hypersensitivity reactions

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Interleukin 2 (IL-2) and lymphokine activated killer (LAK) cells have synergistic antitumour effects in animal models, perhaps via effects on T cell function[1]. The effects of IL-2 on T cell activity are well known, but those of LAK cells are not. This study was designed to investigate the influence of IL-2 and LAK cells on the T cell mediated delayed-type hypersensitivity (DTH) reaction.

Four groups of 15 C57BL/6 mice were sensitised to 2,4-dinitrochlorobenzene by footpad painting, then rechallenged 6 days later. Footpad weight was measured 48 h after second exposure to allergen. Control animals (group A) were compared with animals given IL-2 at 15 000 units i.p. TID (group B), animals given one i.v. dose of 10^8 LAK cells (group C) and animals given both treatments (group D). All treatments were begun 1–3 days before rechallenge.

Treatment with IL-2 enhanced the DTH response, whilst LAK cells had little effect. The combination of LAK cells and IL-2 elicited a significantly weaker response than did IL-2 alone (see *Table*).

	Group A	B	C	D
Mean increase in footpad weight (%)	18·0	44·0	17·97	29·55

P(treatment effect)$= 0{\cdot}0029$ (ANOVA), $P < 0{\cdot}05$ B versus D (t-test)

LAK cells have unexpected inhibitory effects on the DTH response. Further studies are required to determine the mechanism underlying these findings and their relevance to IL-2 based cancer immunotherapy.

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Effect of somatostatin on serotonin-induced intestinal secretion

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Somatostatin (SMST) reduces some of the symptoms in patients with the dumping syndrome, but is not effective in the diarrhoea of this disorder. Serotonin (5-HT) secretion, stimulated by rapid small intestinal transit of hyperosmolar substances, mediates this secretory diarrhoea. Our hypothesis was that this effect of serotonin is mediated via an enteric mucosal 5-HT receptor not antagonized by SMST. Guinea-pig small intestinal mucosal sheets were mounted in flux chambers under short circuit conditions. Membrane viability was assessed by recording change in conductivity (ΔG) and response to 1 0M mucosal dextrose. Short circuit current (I_{sc}) is a sensitive indicator of ion transport (flux) and was recorded at equilibrium (baseline) and in resonse to 10 μM serosal 5-HT, 0·01 μM SMST and 0 01 μM of the 5-HT$_2$ antagonist ketanserin (Ket). The effect of SMST and ketanserin on 5-HT-stimulated I_{sc} was then recorded.

		I_{sc} (μA/cm^2)			
	n	Baseline	1 min	5 min	10 min
Control	5	20 7±0·6	20 9±0·6	20 0±0·6	19·8±0·8
5-HT	5	18 6±2·5	50·0±5·1	49·0±3·5	44·8±2 5
SMST	5	23·6±5·5	11·7±3 8**	11 0±4 1	10·2±4 5
Ket	3	22·4±1·5	22·8±2·1	22·3±1·3	22 0±1·8
5-HT+SMST	5	16 2±1·4	48·2±4·1	44·8±2·8	44·8±2·5
5-HT+Ket	5	23 8±0 1	22 8±0·3*	24·9±0 1*	23·8±0 2*

Results are means±s.e.m.. * $P<0·01$ versus 5-HT (ANOVA for serial measurements); ** $P<0\ 01$ versus baseline (paired *t*-test)

The results (*Table*) reveal that SMST inhibited baseline but not 5-HT-stimulated I_{sc} Ketanserin had no effect on basal I_{sc} but significantly inhibited 5-HT-stimulated I_{sc}, confirming our hypothesis and raising the possibility of specific antagonist therapy in the management of patients with refractory diarrhoea in the dumping syndrome.

Clinical significance of cell kinetics in head and neck cancer

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Survival for patients with advanced head and neck cancer treated with Cisplatin is related to tumour DNA content. Those with aneuploid cancers survive a mean of six months longer compared to only six weeks for diploid tumours. This may be due to increased growth fraction in aneuploid tumours and we have investigated this by measuring potential doubling time (T_{pot}) for these tumours following *in vivo* labelling with bromodeoxyuridine (BrdU)

An infusion of 200 mg BrdU was given to patients 8 h prior to surgery. Tumour biopsies were disaggregated and DNA stained with propidium iodide and FITC-labelled anti-BrdU antibody. By measuring the distribution of BrdU-positive cells throughout the cell cycle, T_{pot} was calculated. BrdU labelling index (LI) was also compared with S phase fraction (SPF) calculated from the DNA histogram by a rectangular method.

The LI range was 0·6–12 6 per cent and was on average lower than the SPF (range 2·4–30 per cent) by a factor of 1·5. There was significant correlation between the two calculations of S phase cells ($r=0·7$, $P<0\ 007$). Median doubling time (T_{pot}) was 6 0 days (range 3 4–101), that for aneuploid cancers was 5 9 days, less than half the figure for diploid cancers (20 7 days).

The short doubling time and the high growth fraction in aneuploid cancers may be the explanation for the patients' prolonged survival following effective chemotherapy.

Colonic electrolyte secretion: evidence for an enteric mucosal 5-hydroxytryptamine receptor

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5-Hydroxytryptamine (5-HT) induces secretion in rat colon by stimulation of electrogenic chloride (Cl$^-$) secretion. This can be recorded as change in short circuit current (ΔI_{sc}) in membranes mounted in flux chambers under short circuit conditions Our hypothesis was that this effect is mediated in part by an action of 5-HT on an enteric mucosal receptor. Rat left colon was excised, stripped of muscularis propria (and attached myenteric plexus) and mounted in Ussing flux chambers under short circuit conditions. Histological analysis with a neurone-specific enolase marker confirmed the absence of neural plexi. Change in short circuit current was recorded in response to 100 μM serosal 5-HT, 0·1 μM 5-HT$_2$ antagonist ketanserin (Ket), and 1 μM 5-HT$_3$ antagonist ICS 205–930 (3-tropanylindole-3-carboxylate methiodide, ICS). Ketanserin and ICS had no effect on basal I_{sc} in the absence of 5-HT.

		ΔI_{sc} (μA/cm^2)			
	n	1 min	5 min	10 min	20 min
Control	5	−1 9±1·3	−2·5±0 7	−2·9±0·8	−4 9±1·1
5-HT	5	60 4±9·3	67·2±9·5	38·4±6·8	30·8±2·6
5-HT+Ket	5	25·7±8 4*	22·7±9·5*	18·0±8·3*	24·2±8·6
5-HT+ICS	3	43·8±2 0	54 8±0·5	30·5±5·5	28·6±2·8

Results are means±s.e.m. * 5-HT+Ket versus 5-HT (ANOVA for serial measures)

The results confirm that 5-HT has a direct action on mucosal Cl$^-$ secretion. This effect is antagonized by ketanserin but not by ICS 205–930, suggesting mediation by a 5-HT$_2$ receptor These findings support our hypothesis and raise the possibility of specific antagonist therapy in the diarrhoea of the carcinoid syndrome

Neurone-specific enolase: a biochemical index of severity of brain trauma

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Neurone-specific enolase (NSE) is an enzyme of the glycolytic pathway specific to neurones and neuroepithelial cells We reasoned that its release into cerebrospinal fluid (CSF) and serum may reflect the degree of anatomical brain damage after head injury Twenty one patients were studied with a mean Glasgow coma scale (GCS) of 5·95 APACHE II and injury severity scores (ISS) were obtained together with recovery score at 6 months assessed by Glasgow outcome scale (GOS)

Non-haemolysed serum samples were obtained from 14 patients. Serum concentration of NSE ranged from 16·25–154, mean 85 45 ng ml^{-1} Non-haemolysed CSF samples were obtained in 11 patients with NSE concentration ranging from 1 5–49 5, mean 25·39 ng ml^{-1} Previous work had shown the upper limit of normal to be 13 ng ml^{-1} in control serum, and 1 ng ml^{-1} in control CSF

The values of GCS, APACHE II, ISS, serum and CSF NSE were each plotted against GOS. Spearman rank correlation coefficients were respectively, 0·69 ($P<0·001$), −0·74 ($P<0·001$), −0·58 ($P=0·005$), −0 73 ($P=0\ 003$) and −0 16 ($P=0·64$)

We conclude that a high APACHE II score and high serum neurone-specific enolase within 24 h of injury predict a poor outcome at 6 months

Alternatives to blood transfusion in major surgery

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Homologous blood transfusion is associated with a significant risk of infection and isoimmunization, and used alone is suboptimal in supporting haemostasis following surgery. In order to limit such complications we have employed autodonation techniques using normovolaemic haemodilution immediately before surgery, in association with red cell salvage and autotransfusion on wound closure. We studied twelve patients with Hb >11 g dl^{-1} and normal clotting undergoing abdominal aortic surgery. Following anaesthesia, haemodilution was achieved by removing 20 per cent of blood volume (calculated by height and weight) while simultaneously infusing gelofusin to maintain normovolaemia. A mean of 1100±50 ml blood was withdrawn and stored at room temperature in standard bags containing CPD-A1 anticoagulant. Blood lost during surgery was collected using a cell saver and on wound closure autodonated blood was reinfused. Operative blood loss was determined, Hb, PCV, platelets and creatinine were measured postoperatively. Blood loss was 780±111 ml, and 234±43 ml of cell saved haemoconcentrate was reinfused.

	Pre-op	Recovery	Days post-op		
			1	2–4	5–7
Hb	14·4±0·5	11·5±0·8	11·9±0·7	11·6±1·0	11·5±0·6
PCV	0·42±0·01	0·34±0·02	0·35±0·02	0·35±0·03	0·34±0·02
Platelets	265±33	184±33	170±26	205±61	246±24

Hb, PCV and platelets initially decreased but remained within normal limits as did serum creatinine. Two patients required donor blood and two were given iron supplements. In selected patients immediate preoperative haemodilution and autodonation is safe, simple and effective in minimizing the need for stored blood during major surgery.

Interstitial laser hyperthermic treatment of tumours

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Hyperthermic temperatures (42–44·5°C) have been produced in tumours by ultrasound, radiofrequency waves and microwaves. A Nd:YAG laser with an artificial sapphire probe is an alternative method. Studies on rat liver showed that application of 3 W via the interstitial probe produced tissue temperatures of 44·5°C 5 mm away and this could be used to treat tumours 10 mm in diameter.

Thirty-six CBH rats inoculated subcutaneously with 10^5 HSN fibrosarcoma cells developed tumours 10 mm in diameter, which were either used as controls, treated by surgical excision or treated interstitially with the laser using 3 W for 1200 s or 4 W for 900 s. Thermocouples monitored tumour temperatures during laser treatment. Tumour dimensions were measured regularly and the animals were killed when one tumour diameter was 25 mm or 100 days after inoculation.

Group	*n*	Mean volume (cm^3)	Mean survival (days)	Range	
Control	9	0·42	32	29–36	
3 W, 1200 s	9	0·32	48	29–100	$P<0·05$
4 W, 900 s	9	0·29	65	31–100	$P<0·01$
Surgical excision	9	0·68	100	100	$P<0·01$

This method of producing hyperthermia caused complete tumour regression in 5/18 tumours, 4 W being more effective than 3 W. It could be used to treat inoperable tumours and may be more effective if used in combination with radiotherapy or chemotherapy as the effect may be synergistic.

Use of magnetic resonance imaging in the staging of pelvic urothelial malignancy

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The accurate staging of transitional cell carcinoma (TCC) of the bladder is essential in order to offer the correct treatment to patients with the condition. In particular the detection of invasion into muscle layers or into adjacent organs will affect both prognosis and treatment options available. The value of magnetic resonance imaging (MRI) for staging bladder cancer has been studied.

Fifty-four patients with a diagnosis of TCC of the bladder were studied. In each case MRI scans were obtained in three dimensions (sagittal, coronal and transverse) on a Picker Vista 2500 0·5 Tesla scanner. The spin sequences used included T1, T2-weighted and 'short tau inversion recovery' (STIR).

Clinicopathological data was obtained in each patient and included clinical stage, tumour grade and pathological stage. Pathological stage was assessed by examination of tissue obtained at transurethral resection ($n=39$) or at cystectomy ($n=15$). In 24 cases the tumour was pTa or pT1 (i.e. non-invasive) in 19 cases it was pT2 or pT3 (muscle-invasive) and in 11 cases it was pT4 (invasion through the bladder wall). In 48 cases the MRI scan agreed with the clinicopathological staging. In four cases the MRI scan had understaged the disease and in two cases it had overstaged the disease.

Magnetic resonance imaging offers an accurate method of imaging TCC which has extended beyond the wall of the bladder. There are a significant number of both false positives and false negatives with the main problem being the differentiation of non-invasive from muscle-invasive disease. The use of a contrast agent (gadolinium-DTPA) may improve the results of imaging.

Taurolidine as an anti-neoplastic agent: a previously undiscovered role?

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In a previous study, taurolidine, a chemical anti-endotoxin, produced inhibition of MTT (3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) incorporation in several tumour cell lines. We examined the *in vivo* anti-tumour activity of taurolidine. C57BL/6 mice injected i.v. with 1·5 × 10^8 B16 melanoma cells were treated as follows: with normal saline i.p. three times daily on days 0–10, with 4·0 mg taurolidin i.p. three times daily on days 0–10, and with 4·0 mg taurolidin i.p. three times daily on days 3–10. Mice were killed on day 10 and pulmonary metastases counted. When taurolidin treatments started on the day of tumour injection, the number of pulmonary metastases was significantly reduced compared either to the control group or to group C ($P<0·05$).

Treatment group	*n*	Pulmonary metastases (mean(s.e.m.))
Saline	25	117·3±18·5
Taurolidin (D 0–10)	16	76·4±14·9
Taurolidin (D 3–10)	16	103·5±14·8

In a second *in vivo* model, Balb/c mice injected s.c. with 1·5 × 10^6 Meth A sarcoma cells received either no treatment or taurolidine 2 mg i.p. twice daily for seven days. At seven days, 90 per cent (27/30) of the control animals had palpable tumour growth, while only 40 per cent (12/30) of the taurolidin-treated mice had detectable tumour growth ($P=0·02$). In a third arm, Balb/c mice received i.p. injections of Meth A followed by either 0·1 ml saline i.p. BD or 0·1 ml taurolidine i.p. BP for 7 days. At 7 days, 28/32 saline-treated mice had ascites in comparison to 0/32 of taurolidine-treated mice ($P<0·0001$). Actuarial survival of saline-treated mice was also significantly impaired ($P<0·005$). Taurolidine is capable of inhibiting tumour growth and may be a useful anti-neoplastic agent either alone or in combination with tumour necrosis factor. Clinical studies evaluating the use of i.p. taurolidin at the time of tumour resection are planned.

Selective uptake of lipiodol by liver tumours

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Lipiodol, a derivative of poppy seed oil, has been used angiographically to improve visualization of small liver tumours. We have utilized this finding to determine whether intrahepatic arterial injection of lipiodol can be used as a vehicle to selectively deliver ^{131}I into liver tumours.

Two groups of rats were studied. Group 1 (control, no liver tumour) received 0·1 ml ^{131}I-lipiodol (luCu) into the hepatic artery. Three animals were killed at regular time intervals over 30 days and organs submitted for well-counting. Over 90 per cent of activity remained within the liver at 6 h. Eighty per cent of activity was lost from the normal liver to be excreted in the urine over 30 days.

Group 2 animals received intraportal injections of 7·5 × 10^5 MC28 tumour cells. Multiple liver metastases were present after 14 days. Three animals were studied at each time interval Samples from tumour and liver were submitted for well-counting.

Time (days)	Tumour:non-tumour ratio (mean)
0	4·84
1	5·35
2	9·55
3	2·66
5	1·99
7	2·54
10	0·76

^{131}I-lipiodol was therefore selectively retained within tumour and cleared from normal liver.

Two patients have received ^{131}I-lipiodol at hepatic artery angiography prior to resection to solitary liver metastasis. Samples of the resected specimen demonstrated a tumour to non-tumour ratio of 2.1 at 24 h and of 4:1 at 5 days.

^{131}I-lipiodol may prove valuable as a delivery agent for radio/chemotherapy to liver metastases

Similarity of mutagenesis in pancreas and colon

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Carcinoma of the colon and pancreas are common in Western societies and the prevalence of both is closely related to average daily fat consumption Mutations of the Kirsten-*ras* oncogene have been reported in both cancers, and the overexpression of the oncogene product p53 occurs in ≈50 per cent of colon cancers. In this study the mutation of Kirsten-*ras* oncogenes and the expression of p53 was investigated in tissue samples from patients with adenocarcinoma of the pancreas. To detect mutations at codon 12 of the Kirsten-*ras* oncogene, DNA was extracted from frozen biopsies using a proteinase K digestion, amplified using the polymerase chain reaction, and the product digested with the restriction endonuclease *Bst*NI. Expression of p53 was determined by staining frozen sections with the anti-p53 monoclonal antibody pab421. Mutations of Kirsten-*ras* were detected in 10/19 (57 per cent) of samples, and there was a significant relationship to the presence of metastases ($P<0\cdot05$, Fischer exact probability test). Nuclear staining with the p53 antibody was observed in 2/12 (17 per cent) of cases.

Although we report here small numbers of pancreatic adenocarcinomas, our results indicate that the same molecular abnormality appears to occur in these two gastrointestinal carcinomas, raising the possibility of a common aetiology

Effect of warfarin and factor VII on tissue procoagulant activity and metastasis

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Warfarin inhibits metastasis in several animal tumour models, but whether this is due to its anticoagulant effect, inhibition of tumour procoagulants or a direct cytotoxic effect remains debatable. We have examined the possibility that the anti-metastatic effect of warfarin is related to an effect on the procoagulant activity of normal tissue.

Using a chromogenic assay, the factor-X-activating activity (FXAA) of rat adrenal, lung, liver and colon was measured in animals with and without warfarin therapy. Tissue FXAA was also measured in warfarinized rats following injection of purified factor VII (FVII) Finally, the correlation between changes in lung FXAA brought about by these manipulations and its ability to support metastatic MC28 cells was analysed.

Tissue	FXAA	Control	Warfarin
Adrenal	13·0	(8·5–22·0)	0·7 (0·3–1·5)*
Lung	6·4	(5·4–11·4)	2·3 (1·2–2·9)*
Colon	0·5	(0·2–0·8)	0·1 (0·1–0·3)*
Liver	0·8	(0·3–1·9)	0·3 (0·2–1·1)

Results are expressed as median with interquartile range in parentheses, *$P<0\cdot001$

Injection i.v. of FVII into warfarinized rats significantly increased FXAA ($P<0\cdot001$) in adrenal and lung, but not colon or liver. Rats given warfarin had significantly fewer ($P<0\cdot001$) pulmonary metastases (median =0·5, range 0–15) after i.v. MC28 than controls (median =0·7, 0·31) or warfarinized rats given FVII at the time of MC28 injection (median=6, range 1–26).

It is concluded that warfarin reduces the procoagulant activity of normal lung tissue and that this is paralleled by a reduction in MC28 metastasis. This mechanism may explain the role of warfarin in reducing metastatic spread.

Correspondence

Prognosis in colorectal adenocarcinoma

Sir

Dr Enblad *et al.* (*Br J Surg* 1990; 77. 611–16) are to be congratulated on the extensive number of patients studied and the clarity of their recent report on survival from colorectal cancer. This must surely be the largest and best documented study on the subject. Their conclusion that patients below the age of 40 years with adenocarcinoma of the colon and rectum have a prognosis similar to that of patients above that age is entirely correct on the data supplied, but this is an oversimplification of the circumstances and could be misleading. Their data clearly show that the worst prognosis from adenocarcinoma of the colon was in those aged under 20 years (44.7 per cent in men and 33.4 per cent in women) and that this also extends to those aged 20–29 years (46.6 per cent in men and 34.0 per cent in women). In addition, they also showed that the worst prognosis for any colorectal tumour was seen for adenocarcinoma of the rectum in men aged 20–29 years (28.7 per cent). It was also interesting to note that the prognosis from colonic adenocarcinoma was worse in women under 30 years, whereas prognosis from rectal tumours was worse in men under 30 years.

Adenocarcinoma of the colon in those under 20 years demonstrates a number of features that distinguishes it from the adult equivalent and although it is rare, the prognosis is poor[1,2]. The poor prognosis of these tumours in those under 20 years is attributed to the late stage at presentation, frequently with local invasion and distant lymph node or multiple metastases[1–3]. In addition, up to 80 per cent of colonic neoplasms in young people are poorly differentiated, mucin-secreting tumours with a signet-cell morphology which is also associated with a poor prognosis[1,2,4].

Although the authors may well be correct in what they state, more detail would be welcome concerning their young patients. Division of their patients at 25 or 30 years rather than 40 years may modify their conclusion regarding prognosis from adenocarcinoma of the colon and rectum in agreement with many other studies on the subject.

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Authors' reply

Sir

We thank Dr Holdsworth for his considerations which we found relevant. The prognosis of young patients with colorectal cancer has been the topic of many investigations over the years. Most studies have focused on patients under the age of 40 years and that was the reason why we studied this group of patients. Furthermore, many authors have postulated that young patients with colorectal cancer have a worse clinical outcome despite the fact that the number of patients studied have been too small to allow statistically valid conclusions. In order to obtain a group of patients large enough to permit meaningful statistical comparison we found it feasible to divide the patients at the age of 40 years. Although, the survival figures for patients under 20 years of age indicate that children and adolescents might have the worse prognosis, we do not agree with Dr Holdsworth that this is clearly illustrated by our results since 12 patients only were under the age of 20 years. It is essential not to overemphasize the importance of that observation, especially since our impression is that far too many studies on this topic draw conclusions from insufficient numbers of patients. Unfortunately, The Swedish Cancer Registry does not include clinical data such as grade and stage which would have been valuable in order to substantiate the previous findings that young patients present at a later stage and show different microscopical features.

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Prospective study of colorectal cancer in the West of Scotland: 10-year follow-up

Sir

It is interesting to note in the paper by C. S. McArdle *et al* (*Br J Surg* 1990; **77**: 280–2) that the level of surgery performed is suboptimal. This in a developed country with the finest tradition of surgical training. The authors conclude that colorectal cancer surgery be undertaken only by surgeons with a specific interest. Increasingly other authors[1] draw similar conclusions about other procedures.

In this small mission hospital we undertake colectomies, pancreaticoduodenectomies and oesophagogastrectomies for cancer. Our numbers are too small to draw conclusions other than the fact that we certainly qualify for the label of the 'occasional operator'.

Much time and resources are expended in the training of surgeons who cannot all be employed in pursuing specific interests in large teaching hospitals. Surely such training should encompass all the technical expertise and attention to detail required to deal with these surgical challenges, or else the training programme is wasteful and inappropriate.

While specialization is inevitable is 'one man, one procedure' a desirable or indeed a feasible goal?

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1. Bancewicz J. Cancer of the oesophagus. *Br Med J* 1990, **300**: 3–4.

Cancer of the colon and rectum

Sir

I write to comment on your 'For debate' article (*Br J Surg* 1990, **77**: 1063–5). Whilst in the main the consensus views are sensible and balanced, it does contain one complete inaccuracy. This is the statement that. 'There is no formal organization for colorectal surgery in the United Kingdom ...' The colorectal surgeons have met together for many years, but on 9 March 1990, The Association of Coloproctology of Great Britain and Ireland was inaugurated and has a substantial and growing membership.

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Diagnosis and management of mesenteric infarction

Sir

We read with interest the informative article by Mr Clavien (*Br J Surg* 1990; **77**: 601–3). However, in this overview of the subject there is a notable omission with regard to the management of patients with embolic mesenteric occlusions. That is, investigation to locate the origin of the embolus.

The same author has reported that 41 per cent of patients with mesenteric infarction have embolic occlusion of the superior mesenteric artery[1] and it is this group of patients who have the most favourable outcome following surgery[2]. The left side of the heart is the most common detectable origin for such emboli and clinical assessment may indicate valvular disease, endocarditis, an arrhythmia or recent myocardial ischaemia or infarction: all of these may require prompt appropriate treatment. In the otherwise asymptomatic patient, in sinus rhythm, especially if younger than the usual elderly population with mesenteric infarction, the possibility of an atrial myxoma should be considered[3]. Two-dimensional echocardiography is a sensitive method for detecting such tumours[4]. In addition any material removed at embolectomy should be submitted for histological examination[3].

We would suggest that two-dimensional echocardiography is indicated as a routine investigation in all patients with embolic mesenteric occlusion in that it will aid the diagnosis or evaluation of all the potential cardiac pathologies involved. Urgent cardiac surgical intervention is indicated in patients with intracardiac tumours and in a proportion of those with large intracavity thrombi.

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Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis

Sir

The interesting article by J. Byrne *et al.* (*Br J Surg* 1990; **77**: 1046–9) prompts us to write We are in the process of reviewing a similar series and would like to endorse many of the observations made.

In our own study patients showed a 95 per cent improvement if only their hands were involved; however, this fell to 77 per cent if the axillae were also affected. We also found a fairly high incidence of compensatory sweating (75 per cent out of a total of 50 patients). Additionally 48 per cent of our patients mentioned gustatory sweating, often with a 'phantom' component, particularly in response to cheeses and spicy foods, although this did not cause any marked disability. One patient developed a transient bilateral Horner's syndrome, but this complication is unusual as the first rib is not seen transthoracically. The incidence of other complications was gratifyingly low. The majority of our patients were discharged after an overnight stay.

We would, therefore, agree that, both in terms of surgical efficacy and cost, the endoscopic route should become the method of choice for thoracic sympathectomy.

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Evaluation of herniography in the diagnosis of an occult abdominal wall hernia in symptomatic adults

Sir

We would like to support the conclusion of C Hall *et al* (*Br J Surg* 1990; **77**: 902–6) that herniography is useful in the diagnosis of occult abdominal wall hernia in symptomatic adults We have been using this technique in Portsmouth since January 1986 and have now done 54 such examinations without complication.

We have a 2-year follow-up in the first 22 patients. There were eight positive results of which one (one of the first patients), proved to be a false positive. In one of these positive results, the herniogram did not reveal the contralateral inguinal hernia. In the 14 negative investigations, no patient has subsequently developed a hernia at the site of symptoms We have also found the technique successful for demonstrating femoral and Spigelian hernias. Furthermore, in three cases hernias were demonstrated at clinically unsuspected sites.

The exact diagnosis of groin hernia type may be difficult on herniography so the surgeon should be aware that it may be necessary to exclude an adjacent hernia if the expected one is not found at operation.

We conclude that when no physical signs of hernia are present, particularly in the obese, herniography is a safe and reliable procedure to aid diagnosis and helps to select those patients who should have surgical exploration.

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Graduated compression stockings in the prevention of postoperative deep vein thrombosis

Sir

The merits of graduated elastic compression were clearly brought to the forefront in the recent review paper by Jeffery and Nicolaides (*Br J Surg* 1990; **77**: 380–3) However, a review of the details of the references indicates that several errors have been made.

The statements comparing the effects of below knee compression with full leg compression are based on references where the experimental designs limit one's ability to draw the stated conclusions. The use of the ^{125}-I fibrinogen test and the lack of a control group limit its usefulness in drawing conclusions with respect to proximal vein thrombosis[1]. The radioactive tracer velocity measurements of flow parameters from dorsal vein to femoral vein demonstrate significant increases in blood flow velocities for both knee length compression as well as full leg compression[2]. While this work supports the ability of both forms of compression to decrease stasis, it certainly does not reject the benefits of full leg compression in reducing stasis in the proximal veins. The work of Lewis *et al.*[3], using venographic clearance, clearly demonstrated the benefits of proximal compression of the leg in reducing venous stasis in the proximal veins with the experimental focus on the Thigh Length Kendall TED graduated compression stocking. A close examination of the references given for *Table 1* which tabulates efficacy studies on graduated elastic compression stockings in controlled methodologies with objective endpoints is not consistent with the discussion of products described in the text of the review. Of the ten studies listed, eight of the references clearly indicate that the Kendall TED stocking was used In two of the studies, no mention of the specific graduated compression stocking was made; however, in both cases through personal communication, it is acknowledged that the Kendall product was used. Therefore, in the references which support *Table 1*, there is no evidence to support the statement that stockings from American Hospital Supply (CARE), Beiersdorf or Brevet have been demonstrated to be effective in controlled clinical trials. The details from *Table 1* support the conclusion that all of the references presented are based on controlled efficacy studies of the Kendall TED product.

In the references given in *Table 2*, which lack a pure control methodology and assess the combination of graduated elastic compression stockings with other modalities, a review of the experimental methodologies and personal communication with the investigators indicate that Kendall TED stockings were used in all but one of the protocols and this work assessed the addition of the Beiersdorf product to a dextran regimen to enhance the effectiveness of the pharmacological agent

In addition, it should also be noted that the work combining intermittent pneumatic compression (IPC) with graduated elastic compression stockings (Scurr *et al*[4]) utilized full leg sequential IPC, not calf only IPC as the discussion indicates.

It must be clearly understood that not all graduated compression stockings for deep venous thrombosis prophylaxis are the same. While their outward simplicity often lulls one into the trap of assuming they perform the same, in fact effectiveness must be demonstrated in controlled clinical trials with objective endpoints. Of the list tabulated in *Table 1* (controlled efficacy studies with objective endpoints) of the review, only Kendall TED stockings were employed, and this fact should not be confused in the otherwise enlightening review of prophylactic applications of graduated elastic compression

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Truncoumbilical bypass of the portal vein in radical resection of biliary tract tumour involving the hepatic duct confluence

Sir

Kumada *et al.* presented an important improvement in the surgical treatment of hilar bile duct cancer (*Br J Surg* 1990; **77** 749–51) The difference in survival after resections with and without tumour free resection margins is small and most resected patients still die from local tumour recurrence[1] Consequently the current types of resection usually fail to achieve tumour clearance

According to the location of a hilar bile duct cancer an extended area of the hepatic hilus including the complete hepatoduodenal ligament is the minimal requisite for an oncological radical resection. The concept of an extended right hepatic lobectomy including the caudate lobe and the hepatoduodenal ligament, preceded by total hepatic vascular inflow transfer to the left lobe using the umbilical portion of the portal vein, was developed and investigated anatomically and experimentally in the early 1980s[2–5]. Such an operation meets the oncological requisites, provides continuing hepatic and splanchnic bloodflow, allows resection under selective portal and arterial clamping and avoids an all-or-nothing character

A clinical application of such a procedure, using a double portal catheter bypass with temporary arterialization of the hepatic portal system via the dilated umbilical vein but without vascular transfer before resection, was published recently[6] By side clamping of the umbilical portion of the portal vein Kumada *et al.* have now succeeded in constructing a truncoumbilical bypass in paraportal position before the resection. During such side clamping the portal branches to the liver segments II and III have to be spared carefully as the function of the remaining left liver lobe depends on it.

The authors are to be congratulated on their operative achievements Improvement of the long-term results in surgery of hilar bile duct cancer can only be expected from such resections

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5. Boerma EJ, de Boer HHM, van der Heyde MN, van Healst UJGM Hemihepatectomy and replacement of the afferent hepatic blood supply in the dog Resection of liver and hepatoduodenal ligament. *HPB Surgery* 1989; **1** 101–5
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Book reviews

Emergency Abdominal Surgery

R. C. N. Williamson, M. J. Cooper, eds. 195 × 253 mm. Pp 296. Illustrated. 1990. Singapore: Churchill Livingstone £40 00 hardback.

The general surgeon might these days be best defined as that person equipped to deal with the acute abdomen. It is this role which confronts the trend to subspecialization ever earlier in a surgeon's career. Many is the registrar who has rotated back from the district to the teaching centre who has felt himself the best able to manage the emergency work. The self critical will nonetheless acknowledge that on occasions it has by no means been clear what to do for the best treatment in the emergency situation. It is these surgeons that will welcome this book.

The editors are to be congratulated on selecting a powerful international side and for requiring its members to bat on the stickier of wickets. This is not a comprehensive guide to emergency abdominal surgery nor should the space allocated to any particular topic necessarily to be taken to represent its importance in the practical arena. The surgeon looking for clinical guidance should not be dismayed to find in the first section a critical review of Bayesian analysis as an adjunct to diagnosis, but rather should relish the authority with which each author addresses his topic and the light editorial touch which allows the contributions to have a varied and enlivening approach which makes the book a pleasure to read In the aftermath of NCEPOD perhaps there might have been more guidance on the general assessment of patients and the factors that have to be weighed in taking the decision to operate.

This book should be available to all surgeons with responsibility for managing emergency general surgery. Having read it our registrar will still be confronted by problems but should be better informed to the consequences of the decisions that he must make.

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Clinical Oxygen Pressure Measurement II

A. M. Ehrly, W. Fleckenstein, J. Hauss and R. Hugh, eds. 175 × 245 mm. Pp. 436. Illustrated. 1990 Oxford. Blackwell. £110.00 hardback.

The proceedings of two symposia dedicated to clinical oxygen pressure measurements held in Lubeck and Frankfurt in 1988 are presented in this publication. It is said to involve all interested groups but there are noteable omissions. The contributions are predominantly of German origin.

This is an embryonic and exciting field of development and there is great promise in the value of subcutaneous oxygen measurements in the critically ill and for monitoring on ICU. Sadly this book presents little of this application but there are nevertheless good background chapters on the history and physics of oxygen pressure measurement. There are useful chapters on methods of measurement followed by rather repetitive work on the physiology of tissue oxygenation (mainly in skeletal muscle) The field of applications are also covered: diabetic microangiopathy, arterial disease, malignancy, relation to vasoactive drugs and care of the critically ill There are comparisons made with pulse oximetry and laser Doppler flowmetry but these are with transcutaneous oxygenation (TcP_{O_2}) not with the more accurate and sensitive subcutaneous measurement (ScP_{O_2})

This is a book only for the interested physiologist or those involved in clinical research into oxygen pressure measurement. There is nothing particularly new presented in applied medicine or surgery although there is a wealth of European references at the end of each chapter. I can only recommend it to those with a specific interest in the field who might be disappointed by the content of the book.

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Neonatal Surgery. 3rd edn

J. Lister and I. M. Irving 190 × 250 mm. Pp. 715. Illustrated. 1990. London: Butterworths. £135.00 hardback.

This is the third edition of a well known book of neonatal surgery based on the Liverpool experience. There is overall excellence of the text and it is very easy to read. There are excellent general chapters at the beginning with comprehensive references and practical comments about the surgery performed (it is a pity that the references had not been thoroughly checked) I found the chapters on radiology, low birth weight babies and antenatal diagnosis particularly good.

I am uncertain whether the Liverpool experience adds to the text and at times the case numbers do appear rather parochial and anecdotal I think it is a pity that the authors have concentrated on neonatal surgery as it continues the myth that paediatric surgeons only do neonatal surgery! This inevitably means that certain problems such as rectal atresia, Hirschsprung's disease and undescended testis are incompletely covered with no discussion about the definitive treatment Perhaps it should be called 'Neonatal and Infant Surgery' which would cover these objections Some chapters, e.g. congenital heart disease, do cover such areas.

In the 10 years or more since the previous edition, changes and improvements have occurred and so certain chapters have been dropped or changed. Surely the chapter on specialized nursing techniques should have been retained. The chapters on general operative technique and peritonitis could be better incorporated into the text elsewhere.

In contrast short gut problems and intravenous feeding are dismissed in a couple of pages and I think 'complications following surgery' in the newborn warrants more than that. Information on neonatal diagnosis and diaphragmatic hernia is out of date and since Milk Plug Syndrome is rarely seen now, it need only be mentioned in passing. There is no mention of pH monitoring in the diagnosis of oesophageal reflux. In the chapter on anorectal anomolies the importance of nomenclature is correctly stressed so that the use of imperforate anus, albeit in quotations, is misleading.

This remains an excellent book for paediatric surgeons rather than general surgeons. The fact that it is contained in one volume (as opposed to two) makes it an attractive addition to one's library.

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Notices and announcements

3–4 January 1991
73rd Meeting of the Surgical Research Society
London, UK
Information Professor J. R. Farndon, Department of Surgery, University of Bristol, Bristol BS2 8HW, UK

18–19 January 1991
Association of Anaesthetists of Great Britain and Ireland Winter Scientific Meeting
London, UK
Information· Miss A. Muir, Administrative Secretary, 9 Bedford Square, London WC1B 3RA, UK

18–20 January 1991
The 27th Head and Neck Course
Liverpool, UK
Information· Professor P. M. Stell, Department of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX

19–20 January 1991
Hong Kong Surgical Forum
Hong Kong
Information Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 January–1 February 1991
Second European Winter Oncology Conference
Meribel, France
Information. IMEDEX B,V, PO Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands

17–19 February 1991
4th Annual Congress of the North American Society of Phlebology
Florida, USA
Information Connie Simms, Executive Director, North American Society of Phlebology, 204 N. El Camino Real, Suite E234, Encinitas, CA 92024, USA

1 March 1991
Aneurysmal Surgery
Bristol, UK
Information· Mr M Horrocks, Department of Surgery, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK

25–26 March 1991
Injury Research Group Meeting
Newcastle upon Tyne, UK
Information Dr R N Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

3–5 April 1991
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Oxford, UK
Information: Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

17–19 April 1991
International Conference on Railway Suicide
London, UK
Information. Professor R. Farmer, Charing Cross and Westminster Medical School, 17 Horseferry Road, London SW1P 2AR, UK

17–20 April 1991
Kocher Symposium: Endocrine Surgery
Berne, Switzerland
Information Mr K Schluep, Johnson and Johnson AG, Rotzenbühlstrasse 55, CH-8957 Spreitenbach, Switzerland

18–21 April 1991
SAGES 1991 Scientific Session
California, USA
Information Program Committee, SAGES, Suite 409, 1271 Stoner Avenue, Los Angeles, CA 90025, USA

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information Dr G Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Parramatta 2151, Sydney, Australia

8–11 May 1991
Melanoma '91, Brighton International Melanoma Conference
Brighton, UK
Information Dr N. Kirkham, Department of Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE, UK

8–11 May 1991
XXVIth Congress of the European Society for Surgical Research and the VIIIth Tripartate Meeting of The Surgical Research Society and The Society of University Surgeons
Salzburg, Austria
Information· ESSR Congress Office, 1st Surgical Department, Landeskrankenanstalten, Mullner Hauptstrasse 48, A-5020 Salzburg, Austria

15–18 May 1991
Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information· American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

20–24 May 1991
Pacific Association of Paediatric Surgeons 24th Annual Meeting
Hong Kong
Information Secretariat, PAPS Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information Secretariat, 4th International Omentum Symposium, Mrs W. J Buys–Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information James F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information. Prof Dr. med. J. Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus. Brettreichstr 11, 8700 Wursburg, FRG

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information. Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information· Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

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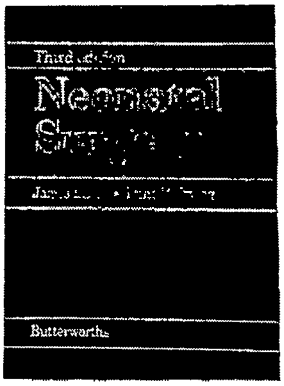

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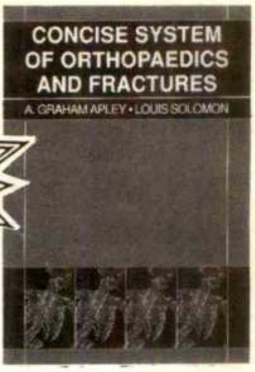
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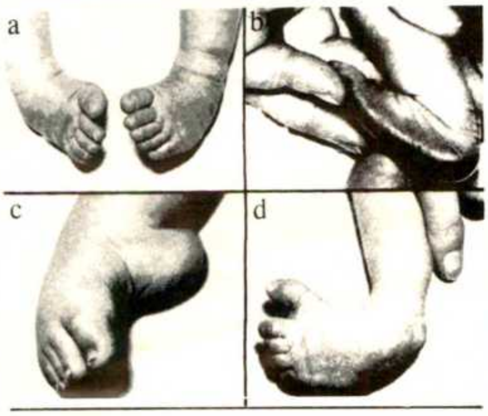

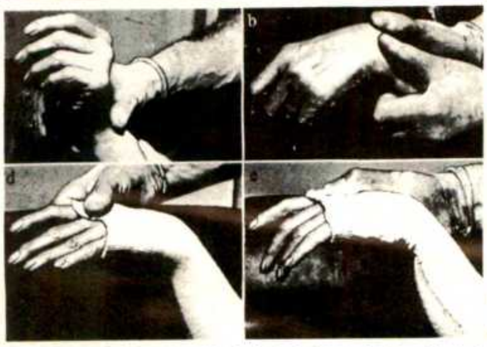

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